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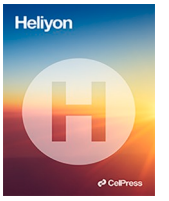

Research article

A bibliometric analysis of the research landscape on vascular normalization in cancer

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ABSTRACT

Tumor vascular normalization profoundly affects the advancement of cancer therapy. Currently, with the rapid increase in research on tumor vascular normalization, few analytical and descriptive studies have investigated the trends in its development, key research power, present research hotspots, and future outlooks. In this study, articles and reviews published between January 1, 2003, and October 29, 2022 were retrieved from Web of Science database. Subsequently, published research trends, countries/regions, institutions, authors, journals, references, and keywords were analyzed based on traditional bibliometric laws (such as Price's exponential growth, Bradford's, Lotka's, and Zipf's). Our results showed that the last two decades have seen an increase in tumor vascular normalization research. USA emerged as the preeminent contributor to the field, boasting the highest H-index and accruing the greatest quantity of publications and citations. Among institutions, Massachusetts General Hospital and Harvard University made significant contributions, and Professor RK Jain was identified as a key leader in this field. Out of 583 academic journals, *Cancer Research* and *Clinical Cancer Research* published the most articles on vascular normalization. The research focal points in the field primarily include immunotherapy, tumor microenvironments, nanomedicine, and emerging frontier themes such as metabolism and mechanomedicine. Concurrently, the challenges of vascular normalization in cancer are discussed as well. In conclusion, the study presented a thorough analysis of the literature covering the past 20 years on vascular normalization in cancer, highlighting leading countries, institutions, authors, journals, and the emerging research focal points in this field. Future studies will advance the ongoing efforts in the field of tumor vascular normalization, aiming to enhance our ability to effectively manage and treat cancer.

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1. Introduction

Tumors heavily rely on angiogenesis to provide the necessary nourishment for growth [1–4]. Tumor cells secrete various pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), and angiopoietin to stimulate the abnormal blood vessels growth, which are characterized by disorganization and increased permeability [5–7]. Consequently, the resulting blood flow is inadequate, leading to a hypoxic microenvironment that fosters tumor invasiveness and compromises drug delivery [8,9]. Anti-angiogenic therapy effectively inhibits tumor growth by disrupting the existing vascular system and preventing the formation of new blood vessels, thereby depriving the tumor of essential nutrients [9]. Numerous preclinical and clinical trials have demonstrated the short-term effectiveness of anti-angiogenic agents in diminishing tumor vessel density, suppressing tumor progression, enhancing the efficacy of concurrent chemotherapy. However, prolonged administration of these drugs has shown limited and transient therapeutic effects, leading to cancer recurrence, the development of an acidic and hypoxic tumor microenvironment, and an increased resistance to anti-angiogenic drugs [10].

Jain proposed "vascular normalization", also known as "vessel normalization", as a way to revolutionize anti-angiogenic therapy to overcome these limitations [11–13]. This theory suggests that an alternative to completely obstructing or inhibiting the growth of tumor blood vessels is to normalize their structure and function through anti-angiogenic therapy. Goel et al. subsequently explained the mechanisms behind tumor vascular normalization, which involves restoring the balance of pro-angiogenic and anti-angiogenic factors in the tumor vascular system [14]. Thus, the concept of a "time window" was established, during which therapeutic drug administration exhibits increased efficacy [15]. Notably, vascular normalization facilitates the organized alignment of pericytes, impeding intravasation and metastasis of tumor cells and improving the overall tumor microenvironment. Therefore, normalization of tumor blood vessels can improve the efficiency of drug delivery, resolve the hypoxic and acidic tumor microenvironment; its application in cancer therapy exhibits potential for enhancing treatment outcomes.

The proposal of the theory of "vascular normalization," along with the official approval of bevacizumab (an anti-VEGF agent) by the Food and Drug Administration (FDA), established the era of tumor vascular normalization. In response, the worldwide scientific community saw an increase in the establishment of research and development facilities and funding programs, contributing to the exponential growth in the field of vascular normalization in cancer exponential growth, with a corresponding increase in related publications. Thus, appropriate and systematic analysis strategies are crucial to explore and synthesize the extensive data being produced, in order to improve our comprehension of the existing knowledge. At present, numerous reviews have been published on the advances and challenges in the tumor vascular normalization field; however, these often lack objective visualized supporting data and depend significantly on researchers' personal interpretation of the disciplinary structure. Therefore, these reviews display a degree of heterogeneity and subjectivity, impeding our ability to thoroughly analyze and determine the current status of research and pinpoint areas of research interest. Bibliometrics is a quantitative approach that uses mathematical and statistical methods to analyze a significant amount of literature in a particular research area in a systematic and unbiased manner [16–18], allows investigators to efficiently obtain the most up-to-date and relevant information in their area of interest. Mainstream bibliometric software, including VOSviewer [19,20], CiteSpace [21,22], and the R package "bibliometric" [23], are tailored to visualize a substantial number of publications, enabling quick understanding of emerging trends in the relevant field. Bibliometric analyses also facilitate the identification of top-notch authors, productive research organizations, reputable research subjects, and influential high-quality publications, thus speeding up the scientific introduction process.

Considering these advantages, this study utilized bibliometric analysis to map out the research landscape on tumor vascular normalization, including publications, countries/regions, institutions, authors, journals, keywords and references. This systematic analysis aimed to establish a comprehensive knowledge base by analyzing the present dissemination of research findings, recognizing key research contributors, locating areas of intense research activity, evaluating the current situation, and investigating the cutting-edge developments in the field. It will serve as a valuable resource for scholars new to the field, guiding them toward interesting avenues for further investigation. Researchers in numerous fields will be able to navigate the breadth of the domain easily with this framework.

2. Research methods

2.1. Data sources and process

This study used data from the Science Citation Index Expanded (SCIE) of the Web of Science Core Collection (WoSCC) on October 29th, 2022. For bibliometric analyses, WoSCC database is considered as the most authoritative and reliable platform; we chose this database as our data source for the following reasons [24–26]: 1) using an integrated databases was crucial to ensure a thorough analysis because our research topic, vascular normalization in cancer, is a multidisciplinary field that encompasses various disciplines, including medicine, pharmacy, and biology; 2) the dataset that was acquired included detailed citation information, facilitating knowledge mapping and empowering us to achieve a more profound comprehension of the interrelationships within the field; 3) The citation reports provided by WoSCC served as a validation mechanism to guarantee the accuracy and reliability of the findings; 4) the datasets did not require format conversion for direct analysis using mainstream bibliometric software, mitigating the potential for data corruption or omitted fields and safeguarding data integrity; 5) the SCIE enforced stringent quality control measures for academic journals and their associated publications; and 6) the inclusion of journals adhered to Bradford's Law, ensuring that core publications were effectively captured and limiting any potential omissions.

The study used wildcards to enhance retrieval strategies and generate a more organized and scientific output. The search strategy

employed in our study involved the following steps: 1) TS=(vascular normalization OR vessel normalization); and 2) TS=(tumo$r* OR sarcoma* OR cancer* OR carcinoma* OR malignana* OR neoplas*). The ultimate dataset = 1) AND 2). The retrieval range for the study was between January 1st, 2003, and October 29th, 2022. The original research articles and literature reviews written in English for inclusion in this study, whereas literature not in English and irrelevant papers such as letters, meeting abstracts, early access, proceedings papers, news items, book chapters, editorial materials, retracted publications, retractions, and corrections were excluded. The study incorporated a total of 1602 publications focusing on vascular normalization in cancer, encompassing 1268 original research articles and 334 review articles. All 1602 manuscripts, along with their respective references, were downloaded and saved as plain text files named "download_txt." Fig. 1 illustrates the thorough process of searching and selecting. The specific process of searching and selecting is shown in Fig. 1.

2.2. Visualized analysis

The following bibliometric laws were applied: Price's law to estimate the annual rate of publications [27], Lotka's law to identify the most prolific authors [28], Bradford's law to find the core journals [29], and Zipf's law to estimate the most relevant keywords in the dataset [30]. Additionally, the H-index measures the impact of scientific research [31], it represents a scholar with at least H publications and at least H citations.

VOSviewer (version 1.6.19, obtained from http://vosviewer.com/) was used to visualize the cooperation network of countries/regions, institutions, authors, journals, and the co-occurrence of keywords and the co-citation of authors [19]. In the map, various nodes correspond to countries/regions, authors, journals, and author keywords. The node size indicates the quantity of publications, occurrence frequency, or citation count; the colors reflect different clusters or timeframes; the thickness of the lines indicates the intensity of the link, which is assessed using the total link strength (TLS). TLS serves as a comprehensive indicator of overall cooperation and co-citation among countries/regions, institutions, or authors.

CiteSpace (version 6.1.R4/R6, obtained from http://sourceforge.net/projects/citespace/), is a recognized and comprehensive software for overseeing knowledge domain visualization [21]. We used CiteSpace to analyze co-cited references, timeline maps, top 15 references with the strongest citation burst, and dual-map overlay of citations.

R (version 4.2.3), specifically the R-bibliometrix package (version 3.0.3, obtained from http://www.bibliometrix.org/), was used to analyze global geographic distributions, H-indices of authors and journals, prolific authors according to Lotka's Law, and core journals according to Bradford's Law. Biblioshiny, a platform providing a web-based interface for R-bibliometrix, was utilized to import data from the WoSCC database and perform visualization analyses. A scientometric web-based platform (http://bibliometric.com/) was employed to generate network visualizations map showcasing international collaborations among countries/regions. Additionally, Microsoft Excel, GraphPad Prism 6 software, and Origin 2022 were used to construct some of the figures.

3. Results

3.1. Publications output and citations

Based on our search criteria, a total of 1696 publications focusing on vascular normalization in cancer were published between

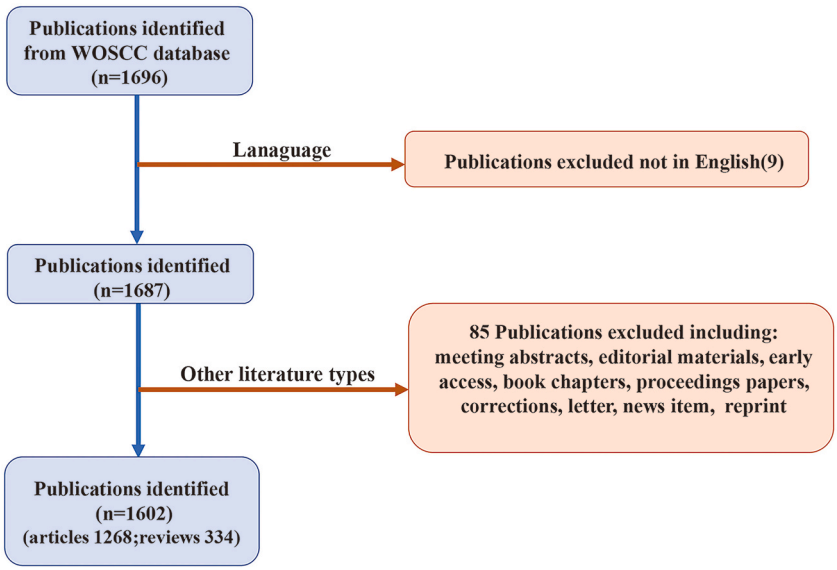


Fig. 1. Flowchart of the publications search and selection process.

2003 and 2022 in the WOSCC database. After excluding inappropriate papers, 1602 publications, including 1268 articles and 334 reviews were ultimately extracted (Fig. 1). In Fig. 2, over the last two decades, the output of annual publications on vascular normalization in cancer has steadily grown, only a few time points showing deviation, reaching a peak in 2021 (n = 150, 9.36%), and the output of annual publications in 2021 was almost 15 times that of 2003 (n = 9, 0.56%). We confirmed that the growth of the vascular normalization field followed Price's Law, with the exponential curve between 2003 and 2021 being defined by the equation $y = 13.434e^{0.1474x}$. Notably, the output of scientific publications in the field increase dramatically from 2000 to 2016, with slight yearly fluctuations; however, this growth decreased below Price's curve after 2017, especially in recent years. As of October 29, 2022, 124 papers were published in 2022. In total, the extracted publications were cited 90,121 times, which reduced to 80,252 after the removal of self-citations, with an average of 56.26 citations per article and H-index is 131.

3.2. Distribution of countries/regions and academic cooperation

In this study, 62 nations have participated in the field of tumor vascular normalization; Table 1 and Fig. 3A present details of the top 10 countries/regions. The United States of American (USA) ranked first in research productivity, with 540 publications and 54,187 citations. The mean quantity of citations each publication was 100.33, and the H-index was 103. China closely followed with 384 publications and 10,240 citations. The mean quantity of citations each publication was 26.67, and the H-index was 50. Third was Germany with 145 publications and 9271 citations; the mean quantity of citations each publication was 63.94, and the H-index was 49. Notably, USA contributed to almost half of the total citations among the top 10 countries/regions. Furthermore, USA exhibited superior citation per article and H-index, compared to other countries/regions. These data demonstrate the preeminence of USA in the field of vascular normalization in cancer. Fig. 3B illustrates the annual publication output trends of the leading 10 countries/regions from 2003 to 2022. USA produced the greatest annual quantity of publications until 2017, when China surpassed them. Fig. 3C presents a geographical distribution map according to the cumulative quantity of publications from each country; these were primarily published in North America, European, and Asia nations. Fig. 3D represents the collaborations between countries/regions, the thicker lines indicating stronger connections and increased cooperation. USA most frequently cooperated with other countries/regions in the field, followed by China. Additionally, Germany had the strongest connection with the USA. Fig. 3E reveals the 38 nations that were included in analyzing global collaboration using VOSviewer, with a minimum threshold of >5 publications. TLS represents the thickness of the lines connecting nodes, indicating the strength of international cooperation; the leading three countries with the highest TLS were USA (TLS = 314), Germany (TLS = 156), and China (TLS = 129).

3.3. Most active and productive institutions

During the study period, 1916 institutions participated in the field of vascular normalization in cancer. Table 2 provides an overview of the leading 10 institutions according to their quantity of publications; these institutions collectively contributed 645 publications, accounting for 40.26% of the extracted articles. Massachusetts General Hospital was the largest contributor with 85 (5.31%) articles; second and third were Harvard University and Harvard Medical School, with 71 (4.37%) and 35 (2.18%) total articles, respectively. Regarding as citations, Harvard University ranked first with 26,690 citations and an average of 375.92 citations per article; Massachusetts General Hospital was second with 25,672 citations and an average of 302.02 citations per article. Among these leading 10 institutions, four were from USA and the others from China, England, Belgium, and Cyprus. Fig. 4 depicts the cooperation visualization network map of institutions that have published >5 publications in the field, generated by VOSviewer; institutions with no connections were excluded from the visualization, and the links between institutions represent their cooperative relationships. A total of 170 institutions were represented in the network, categorized into 14 clusters according to the intensity of their collaboration. The largest node in terms of size and TLS was Massachusetts General Hospital, with 85 publications and a TLS of 165. Thus, the articles published by Massachusetts General Hospital had the greatest influence, despite this institution ranking second in citation count and

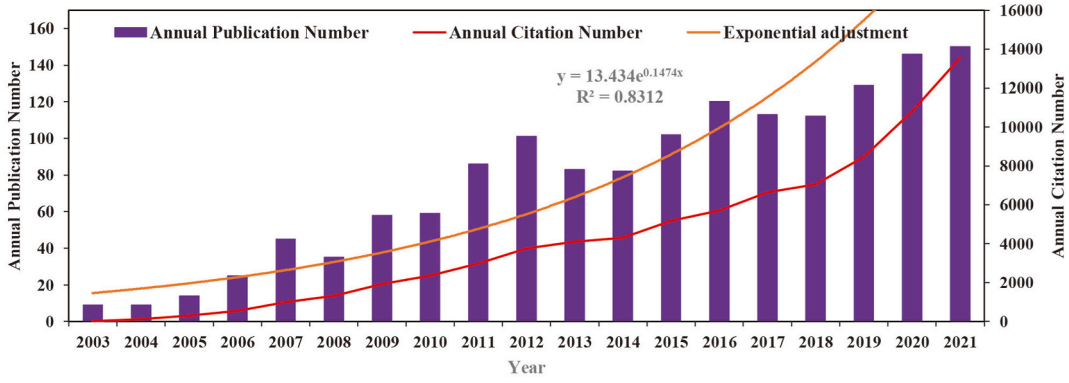


Fig. 2. Number of annual publications and citations related to vascular normalization in cancer from 2003 to 2022. A fitting of an exponential growth curve to the annual publication data was performed based on Price's Law.

Table 1
The top 10 countries/regions contributing to vascular normalization in cancer.

Rank	Country/region	No. of publications	No. of Citations	Citations per article	H-index	TLS
1	USA	540	54187	100.33	103	314
2	CHINA	384	10240	26.67	50	129
3	GERMANY	145	9271	63.94	49	156
4	JAPAN	110	3328	30.25	32	75
5	ITALY	97	4275	44.07	35	76
6	ENGLAND	95	6918	72.82	37	100
7	FRANCE	85	3111	36.6	29	78
8	CANADA	79	3546	44.89	27	63
9	BELGIUM	71	8742	123.13	36	74
10	NETHERLANDS	60	3905	65.08	34	76

TLS: Total link strength.

citations per article. Stronger connections were noted more frequently between agencies than between nations. Massachusetts General Hospital worked closely with numerous domestic research institutions, such as Harvard University and Harvard Medical School, as well as with organizations from Cyprus, the Netherlands, and other nations.

3.4. Most prolific authors and co-cited authors

Our analysis identified 10,046 principal investigators and 39,381 co-cited authors. According Lotka's Law and calculated by R-Bibliometrix, the proportion of authors who published one article on vascular normalization in cancer was 81.8%, which was higher than the 60% expected by Lotka's Law (Fig. 5A). Table 3 presents the leading 10 published and co-cited authors on tumor vascular normalization. The leading 10 most prolific authors collectively proffered 273 articles, accounting for 17.04% of the extracted publications. RK Jain ranked first with 75 publications and 18,365 citations, followed by DG Duda with 34 publications and 8430 citations and T Sylianopoulos with 30 publications and 4671 citations. The H-index was calculated using Bibliometrix software and used to quantify the impact and influence of a researcher's work. Table 3 shows that RK Jain had the highest influence, boasting an H-index of 59, trailed by DG Duda at 25, and P Carmeliet at 21. Fig. 5B displays the visualization network map of co-authorship. Each node corresponds to an author, with node size indicating the associated quantity of published articles. Links between authors indicate their cooperative relationships. The visualization included 55 authors with >5 papers each, forming 8 author clusters; RK Jain had the most collaborators, primarily with American researchers. In contrast, Chinese investigators had limited cooperation in this field. To analyze co-citations, Fig. 5C shows the network of 277 authors who were cited >30 times. Node size reflects the quantity of citations per author, and links reflect the co-citation relationships between authors; TLS reflects the influence of an author on peers in the field. The author most commonly co-cited was RK Jain (2356 citation, TLS = 53,185), followed by P Carmeliet (813 citation, TLS = 17,361) and J Folkman (556 citations, TLS = 12,085).

3.5. Analysis of core journals and co-cited journals

A total of 583 journals published articles on tumor vascular normalization. Bradford's Law [29] posits that scientific journals can be ranked according to their productivity within a specific research area, which can be categorized into three distinct zones, each containing an equal total quantity of publications. Utilizing the bibliometrix tool, we identified the core zone (referred to as zone 1), which included 27 journals that published 534 (33.3%) articles (Fig. 6A, Tables 4 and 5). The top 10 of these core source journals published 310 papers, representing 19.35% of the total of 1602 publications (Table 4). The journal that contributed the highest quantity of relevant papers was *Cancer Research*, with 53 publications (3.31%), followed by *Clinical Cancer Research* (40 publications, 2.50%) and *PLoS One* (36 publications, 2.25%). These three journals are classified into Q1 and Q2 categories based on the 2021 Journal Citation Reports standards and their respective impact factors. The impact factors of the leading 10 journals spanned from 3.752 to 13.801. Furthermore, *Cancer Research* had the most H-index, with a score of 39, trailed by *Clinical Cancer Research* at 28 and *PLoS One* at 20. Notably, the journal *PNAS* had the highest quantity of citations per article, despite being ranked eighth in terms of the total quantity of publications; this is consistent with its H-index.

Additionally, we charted the annual publication trends of the leading 10 journals to gain a more specific understanding of the changing patterns in the quantity of articles published between 2003 and 2022 (Fig. 6B). The graph reveals that *Cancer Research* exhibited the highest annual growth rate in published articles, followed by *Clinical Cancer Research* and *PLoS One*. The remaining journals also contributed publications throughout the last decade. Furthermore, employing VOSviewer, a co-citation analysis was conducted on journals receiving ≥20 citations. The leading five journals with the strongest TLS were *Cancer Research* (TLS = 470,414), *PNAS* (TLS = 257,362), *Nature* (TLS = 231,260), Cancer Cell (TLS = 228,566), and Clinical Cancer Research (TLS = 218,973), as depicted in Fig. 6C.

3.6. Distribution of journal topics in tumor vascular normalization

The dual-map overlay of journals was constructed as a visual representation of the topic distribution in each journal. Fig. 7 shows

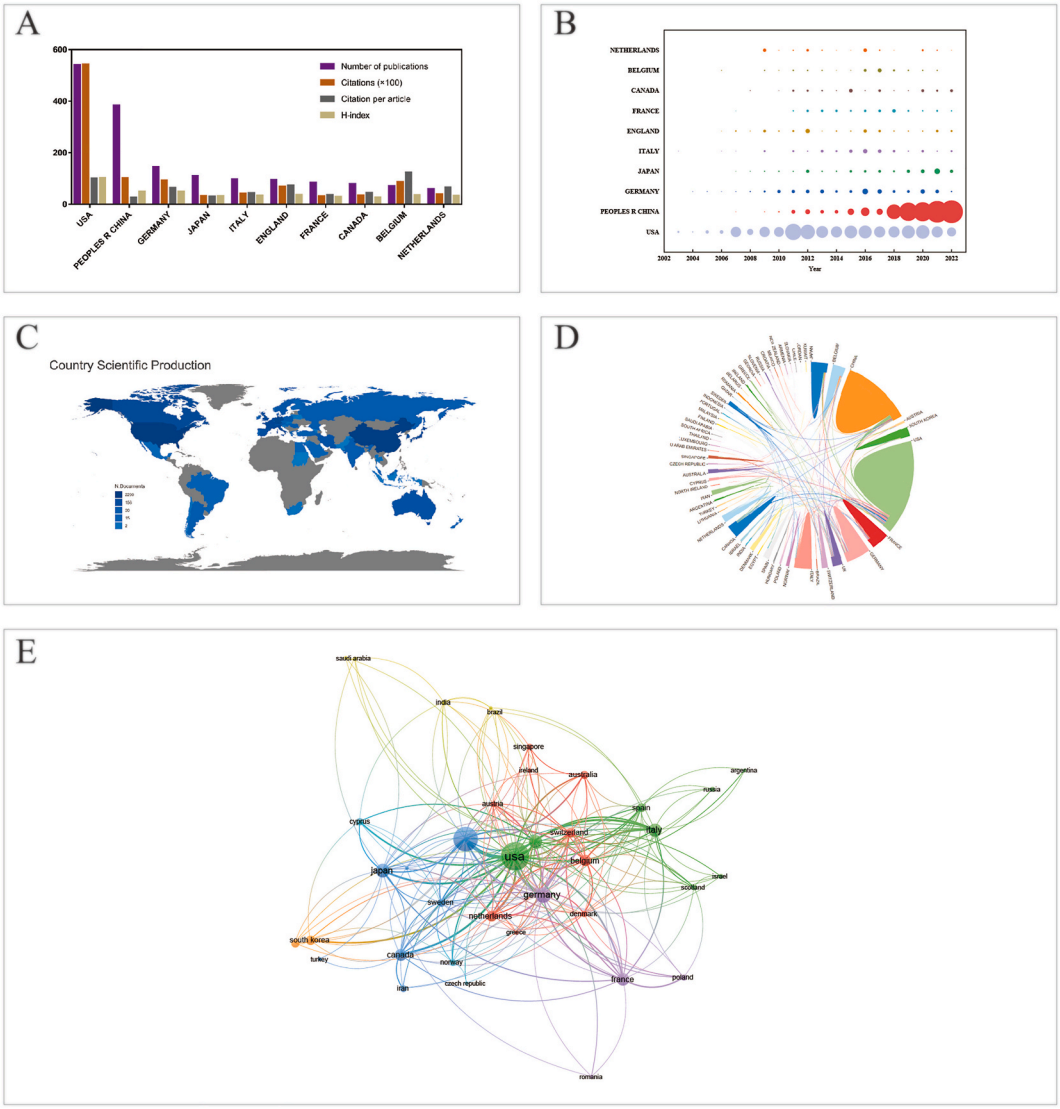


Fig. 3. **(A)** The number of publications, total citations (× 100), average citations per article, and H-index of the top countries/regions. **(B)** The changing trend of the annual number of publications from top 10 countries/regions between 2003 and 2022. **(C)** The geographic distribution map displaying the global distribution of vascular normalization in cancer. Different colors indicate the number of articles published in different countries/regions. The darker the color, the more the country has published. **(D)** The international cooperation's visualization map of countries/regions in the related field. The thickness of the lines reflects the frequency of the cooperation. The thicker the line, the robuster the cooperation between two countries/regions. **(E)** The countries/regions' citation network visualization map was produced by VOSviewer. Different node represents different countries/regions, and the size of the node represents the number of publications. The lines between the nodes reflects a citation relationship, and the thickness of the lines reflects the citation strength. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the dual-map overlay of citing and cited journals, with three main reference paths, represented by green and orange lines, illustrating the flow of knowledge. Specifically, the citing journals principally focused on immunology, molecular biology, medicine, and clinical research. In contrast, the majority of the cited articles derived from journals whose scope centered around genetics, health, molecular biology, medicine, and nursing.

3.7. Analysis of co-cited references

Table 6 presents a summary of the top 10 co-cited references on tumor vascular normalization; the selected articles were published between 2004 and 2018. Among them, those titled "Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy," authored by RK Jain in 2005, and "Mutual regulation of tumor vessel normalization and immunostimulatory

Table 2
The top 10 institutions with most publications related to vascular normalization of cancer.

Rank	Institution	Country	No. of publications	No. of Citations	Citations per article	TLS
1	Massachusetts general hospital	USA	85	25672	302.02	165
2	Harvard university	USA	71	26690	375.92	129
3	Harvard medical school	USA	35	2617	74.77	70
4	Catholic University of Louvain	Belgium	33	5893	178.58	61
5	Sun Yat-Sen University	China	31	1590	51.29	43
6	University of Oxford	England	30	1446	48.20	23
7	University of Cyprus	Cyprus	28	3630	129.64	59
8	University of Texas MD Anderson Cancer Center	USA	28	2472	88.29	36
9	Sichuan University	China	28	630	22.5	11
10	Fudan University	China	27	566	20.96	34

TLS: Total link strength.

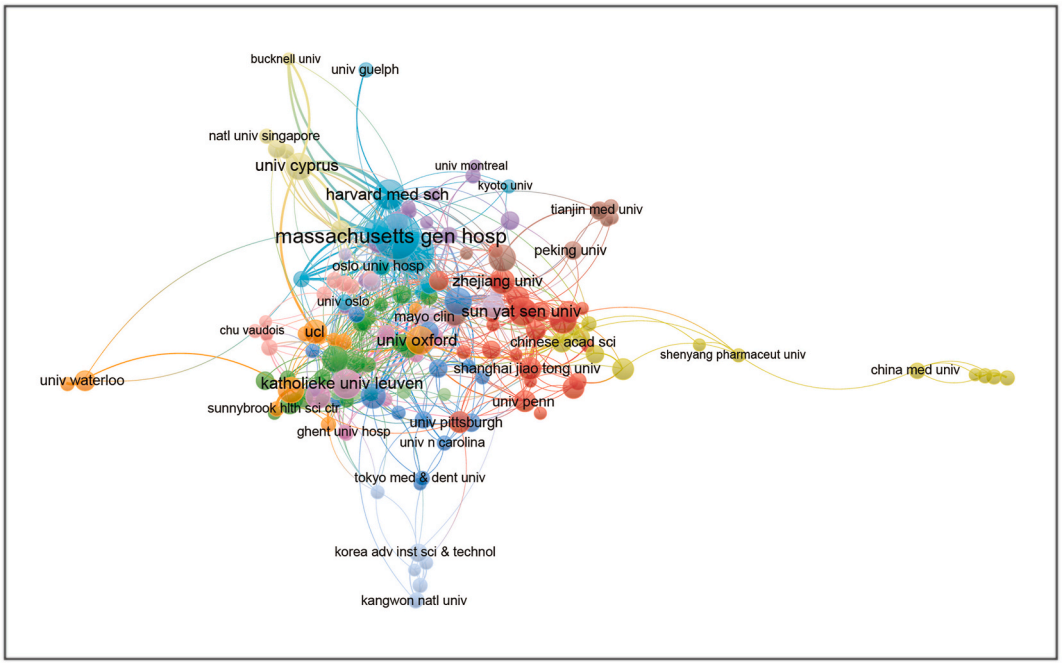


Fig. 4. A cooperation visualization network map of institutions with more than 5 documents on vascular normalization in cancer was produced by VOSviewer. Institutions that had no cooperation with others were excluded from the visualization network map. One node represents an institution, its size represents the number of publications. The links between institutions represents their cooperation relationships in the specific field. The thickness of links represents the intensity of cooperation between institutions.

reprogramming," published by XHF Zhang in 2017, gained the highest quantity of co-citations, with 133 of each article. Moreover, within these top 10 co-cited references, RK Jain is listed as the corresponding author of 8 references.

Employing CiteSpace, we generated a co-cited references network map and the subsequent cluster analysis revealed the existence of 21 distinct clusters (Fig. 8A). The modularity Q value of 0.7309, Mean Silhouette value of 0.8869 suggested that the clustering was valid, as both values exceeded 0.5. The first cluster was labeled "immunotherapy" (#0), demonstrating the relationship between immunotherapy and vascular normalization in cancer. The second cluster was labeled "drug delivery" (#1), indicating a focus on deliverying therapeutic agents. The third cluster was labeled "interstitial fluid pressure" (#2), highlighting the significance of interstitial fluid pressure in vascular normalization.

Furthermore, we constructed a co-cited references timeline visualization map to provide insights into the evolution of the topic (Fig. 8B) [32]. In this visualization, nodes on the same line are distinguished by different colors to represent various years; the leftmost nodes correspond to early references, whereas nodes on the right side represent more recent publications. Our analysis revealed that "interstitial fluid pressure," "acidosis," and "capillary remodeling" were among the earlier topics in the study of vascular normalization in cancer, whereas the current themes focus on "immunotherapy," "metabolism," and "mechanomedicine."

A publication has been commonly cited over a significant period of time as demonstrated by Citation bursts, signifying its importance in the field [33]. We utilized CiteSpace to identify the top 25 publications with the strongest citation bursts. As shown in Fig. 8C, the 2005 article by RK Jain in *Science* [11] had the strongest citation burst, trailed by the 2011 paper by Goel et al. in

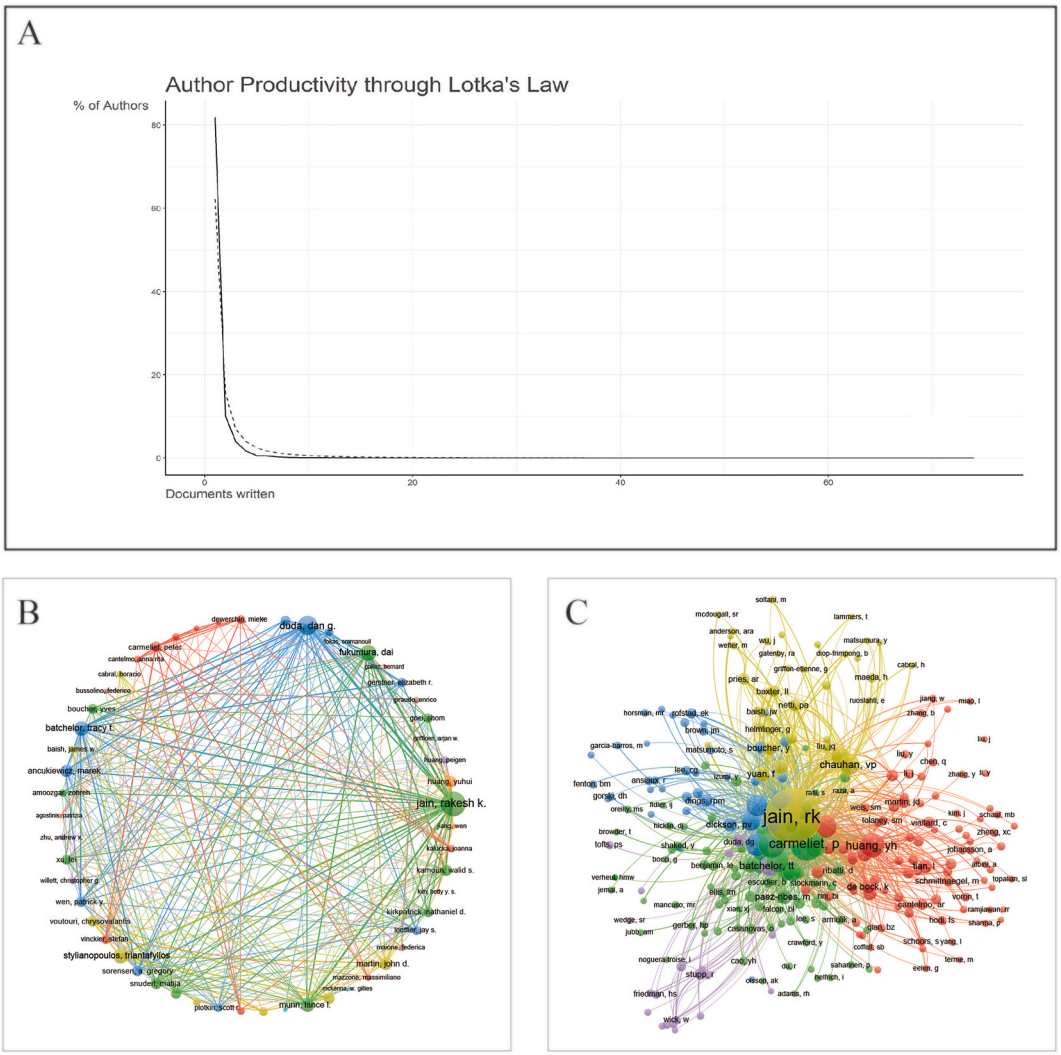


Fig. 5. **(A)** Lotka's Law to calculate the correlation of the number of authors with the articles published (by using R-bibliometrix). Solid black line indicates the distribution of published articles according to the Lotka's law. The dotted line indicates the publication on subject matter. The solid and the dotted lines almost overlap, suggesting the publication trend in vascular normalization in cancer follows the law. **(B)** The network visualization co-authorship map of authors in the field was produced by VOSviewer. One node represents an author, with node size representing the number of documents published by the researcher. The links between authors represent their cooperation relationships. **(C)** The network visualization map of co-cited authors involved in the field was produced by VOSviewer. The size of the node represents the number of citations of author, the links reflects the co-cited relationship between authors. Total link strength (TLS) reflects the influence of author's published papers on other authors involved in specific field.

Table 3
The top 10 most prolific authors contributed to vascular normalization of cancer.

Rank	Author	No. of publications	No. of Citations	Citations per article	H-index	TLS	Co-cited author	Citations	TLS
1	Jain RK	75	18365	244.87	59	269	Jain RK	2356	53185
2	Duda DG	34	8430	247.94	25	166	Carmeliet P	813	17361
3	Sylianopoulos T	30	4671	155.7	20	92	Folkman J	556	12085
4	Carmeliet P	29	6599	227.55	21	51	Huang YH	444	10927
5	Fukumura D	24	6203	258.46	20	113	Winkler F	401	8567
6	Munn LL	18	4708	261.56	15	97	Goel S	374	8323
7	Batcheloe TT	18	4059	225.50	16	78	Ferrara N	354	9013
8	Martin JD	17	3597	211.59	11	72	Tong RT	341	7037
9	Huang YH	16	2049	128.06	15	55	Batchelor TT	297	8870
10	Ganss R	12	839	69.92	9	19	Hanahan D	295	668

TLS: Total link strength.

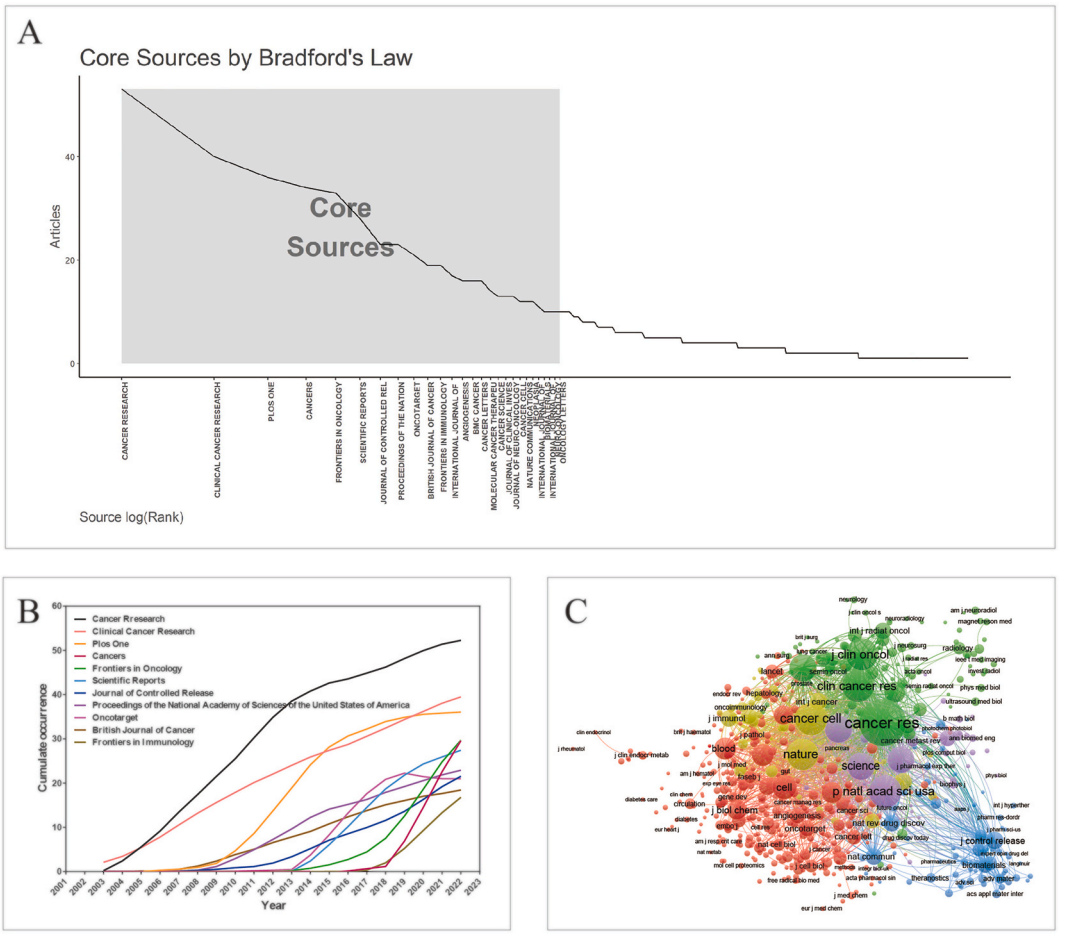


Fig. 6. **(A)** Core source journals analysis according to Bradford's law. Journal rank (on a log scale) against cumulative articles (by using R-bibliometrix). One third of the articles in the field lie in the zone of core journals. **(B)** The changing trend of the annual publication quantity in the top 10 journals created by R-bibliometrix. **(C)** A visualization network map of journals that were co-cited in more than 20 citations was produced by using a VOSviewer. The size of the node represents the number of citations of journal, the links reflects the co-cited relationship between journals. Total link strength (TLS) reflects the influence of journal published papers on other journal involved in specific field.

Table 4
The top 10 core source journals with most publications in zone 1 related to vascular normalization of cancer.

Rank	Journal	No. of publications	No. of Citations	Citations per article	H-index	JCR (2021)	IF(2021)
1	Cancer Research	53	5806	109.55	39	Q1	13.312
2	Clinical Cancer Research	40	2792	69.80	28	Q1	13.801
3	Plos One	36	1370	38.06	20	Q2	3.752
4	Cancers	34	256	7.53	8	Q1	6.575
5	Frontiers in Oncology	33	688	20.85	11	Q2	5.738
6	Scientific Reports	28	660	23.57	14	Q2	4.996
7	Journal of Controlled Release	23	932	40.52	14	Q1	11.467
8	Pnas	23	3490	151.74	20	Q1	12.779
9	Oncotarget	21	739	35.19	17	None	None
10	British Journal of Cancer	19	678	35.68	14	Q1	9.075

Physiological Reviews [15] and the 2004 paper by Winkler et al. in *Cancer Cell* [34].

3.8. Analysis of keywords

According to Zipf's Law, research hotspots can be established through the analysis of high frequency author keywords, allowing readers to quickly identify and prioritize research topics of interest [30]. Fig. 9A shows the scattered distribution curve of keyword

Table 5
According to Bradford's law, the 583 journals were classified into zones 1–3.

Zone	No. of journals	No. of publications	Percentages
1	27	534	33.3%
2	128	541	33.8%
3	428	527	32.9%
Toal	583	1602	100%

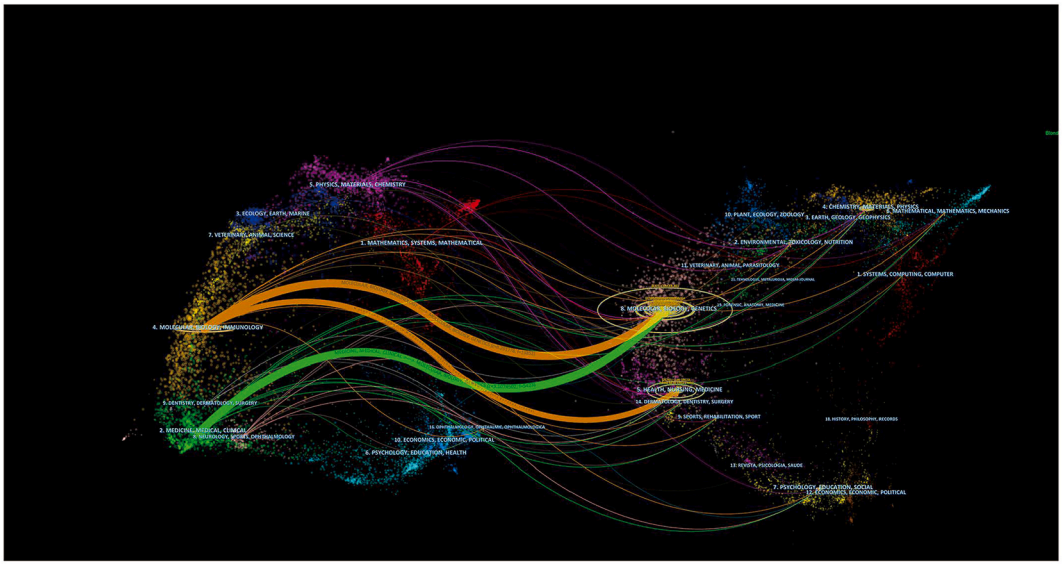
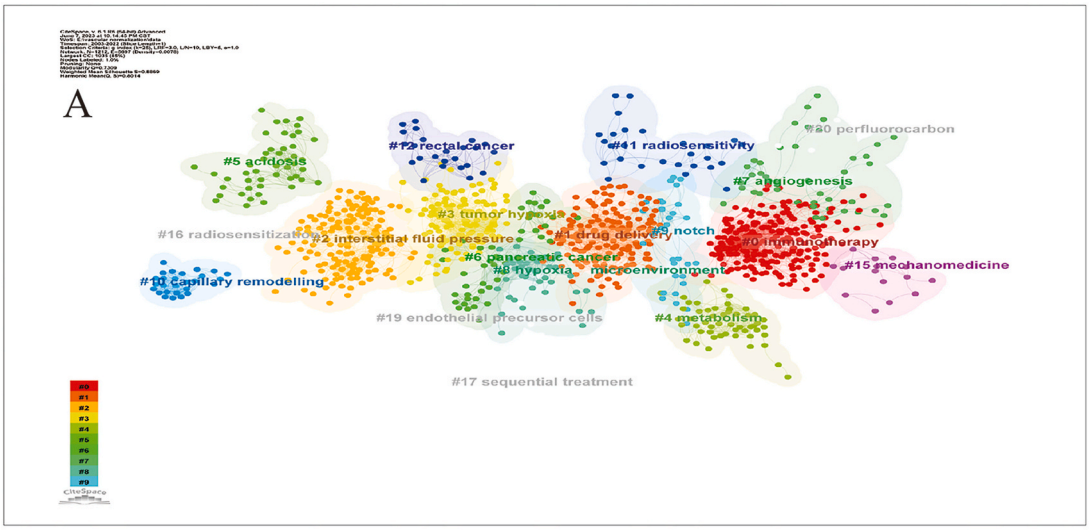
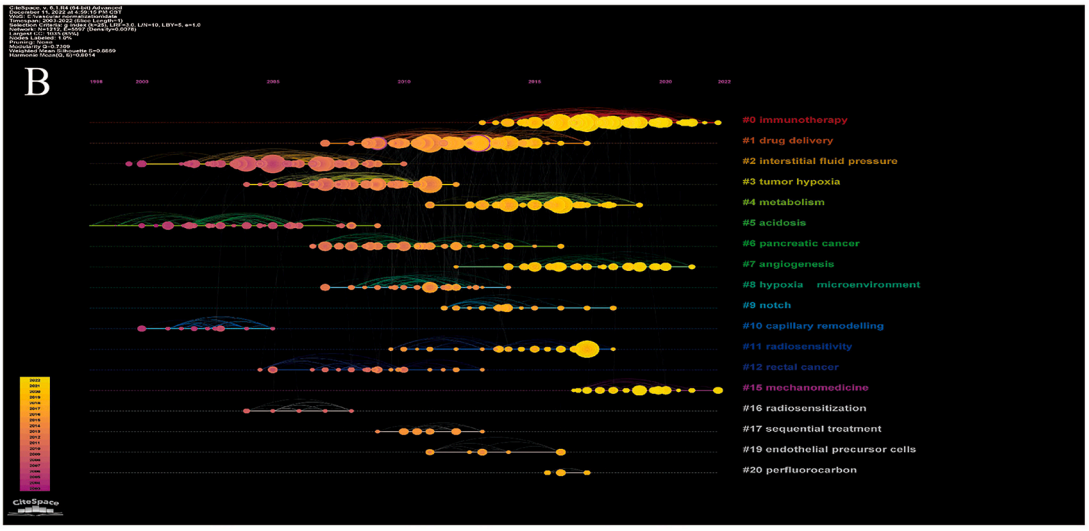


Fig. 7. A dual-map overlay of academic journals related to vascular normalization of cancer produced by CiteSpace software. The left side of the map positions the citing journals, while the right side displays the cited journals. Distinct colored lines illustrate how the citing and cited journals are connected through the reference paths; the width of these lines indicates the frequency of citations, which are represented by z-score scaling to emphasize the strength of the citation relationships.

Table 6
The top 10 co-cited references of vascular normalization of cancer.

Rank	Title	Count	Journal	IF (2021)	CorrespondingAuthor	Years
1	Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy	133	Science	63.714	Jain RK	2005
2	Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming	133	Nature	69.504	Xiang H–F Zhang	2017
3	Normalization of the vasculature for treatment of cancer and other diseases	120	Physiological reviews	46.5	Jain RK	2011
4	Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia	113	Cancer cell	38.585	Jain RK	2014
5	Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases	111	Nature reviews. Drug discovery	112.288	Jain RK	2011
6	Tumor angiogenesis and vascular normalization: alternative therapeutic targets	92	Angiogenesis	10.658	Jain RK	2017
7	Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers	89	Journal of clinical oncology	50.717	Jain RK	2013
8	Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases	88	Cancer cell	38.585	Jain RK	2004
9	Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors	81	Cancer research	13.312	Jain RK	2004
10	Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges	79	Nature reviews. clinical oncology	65.011	Jain RK	2018





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Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	Duration	2003 - 2022
Willett CG, 2004, NAT MED, V10, P145.	2004	23.6	2004	2009	5	
Jain RK, 2005, SCIENCE, V307, P58.	2005	65.5	2005	2010	5	
Winkler F, 2004, CANCER CELL, V6, P553.	2004	46.92	2005	2009	4	
Tong RT, 2004, CANCER RES, V64, P3731.	2004	43.14	2005	2009	4	
Batchelor TT, 2007, CANCER CELL, V11, P83.	2007	30.51	2007	2012	5	
Jain RK, 2007, CANCER RES, V67, P2729.	2007	22.71	2007	2012	5	
Paez-Ribes M, 2009, CANCER CELL, V15, P220.	2009	23.63	2009	2014	5	
Ebos JML, 2009, CANCER CELL, V15, P232.	2009	20.11	2009	2014	5	
Mazzone M, 2009, CELL, V136, P839.	2009	19.72	2009	2014	5	
Goel S, 2011, PHYSIOL REV, V91, P1071.	2011	48.25	2012	2016	4	
Carmeliet P, 2011, NAT REV DRUG DISCOV, V10, P417.	2011	46.53	2012	2016	4	
Carmeliet P, 2011, NATURE, V473, P298.	2011	23.4	2012	2016	4	
Chauhan VP, 2012, NAT NANOTECHNOL, V7, P383.	2012	22.73	2013	2017	4	
Huang YH, 2012, P NATL ACAD SCI USA, V109, P17561.	2012	21.31	2013	2017	4	
Huang YH, 2013, CANCER RES, V73, P2943.	2013	25.05	2014	2018	4	
Batchelor TT, 2013, P NATL ACAD SCI USA, V110, P19059.	2013	20.57	2014	2018	4	
Jain RK, 2013, J CLIN ONCOL, V31, P2205.	2013	34.86	2015	2018	3	
Jain RK, 2014, CANCER CELL, V26, P605.	2014	34.76	2016	2019	3	
Tian L, 2017, NATURE, V544, P250.	2017	40.23	2018	2022	4	
Viallard C, 2017, ANGIOGENESIS, V20, P409.	2017	29.11	2018	2022	4	
Allen E, 2017, SCI TRANSL MED, V9, P0.	2017	20.22	2018	2022	4	
Fukumura D, 2018, NAT REV CLIN ONCOL, V15, P325.	2018	30.27	2019	2022	3	
Schmittnaegel M, 2017, SCI TRANSL MED, V9, P0.	2017	22.48	2019	2022	3	
Huang YH, 2018, NAT REV IMMUNOL, V18, P195.	2018	20.82	2019	2022	3	
Martin JD, 2019, ANNU REV PHYSIOL, V81, P505.	2019	20.42	2020	2022	2	

(caption on next page)

Fig. 8. **(A)** The visualization cluster map of co-cited references was generated by using a CiteSpace. Each circle represents a reference, and circles with the same color represent a cluster with the same topic. **(B)** The visualization timeline view of reference co-cited analysis was generated by using a CiteSpace. The position of each circle on the horizontal axis indicates the time point of the first appearance, the size of the circle represents the total number of it was cited, and the circle on the same line represents a cluster with the same topic. The lines connecting the nodes represent co-cited relationships. **(C)** Top 25 references with the strongest citation bursts were generated by using a CiteSpace. The strength value represents the strength of citation bursts. The red bars indicate the duration of the bursts. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

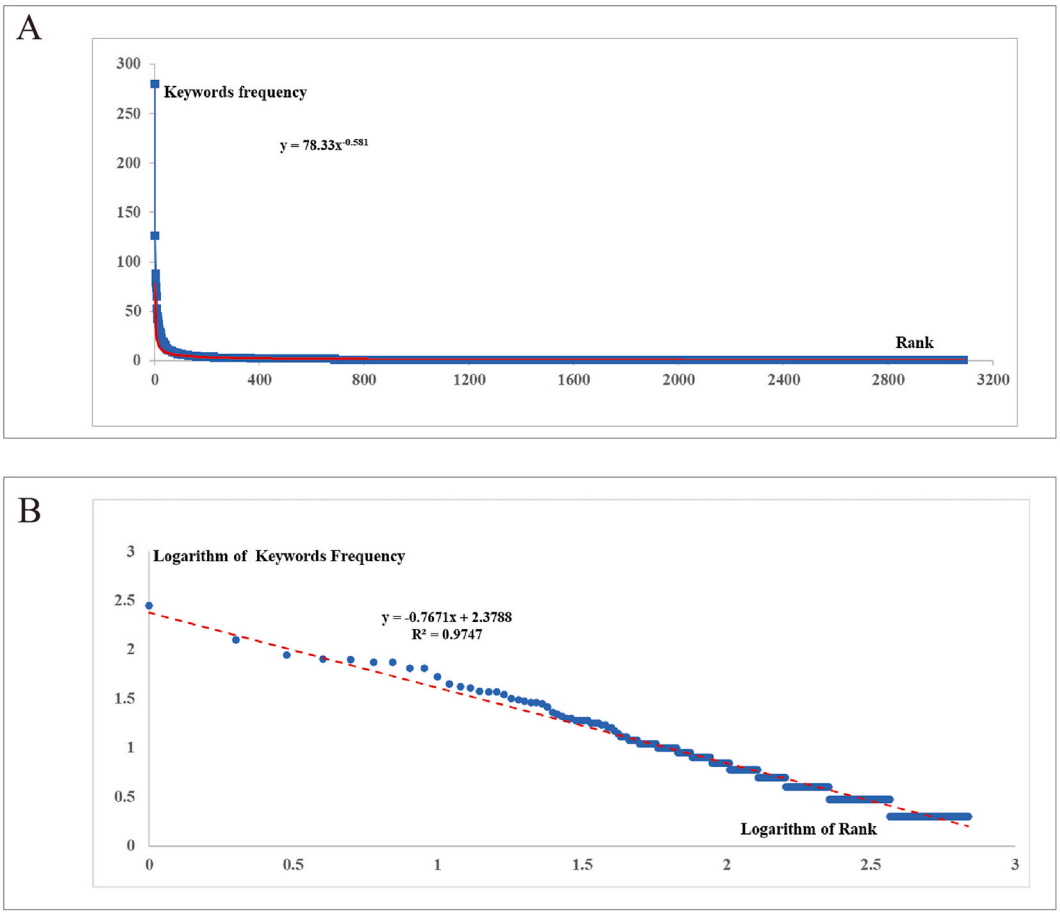

Fig. 9. **(A)** Scattered distribution curve of keywords frequency in the field of tumor vascular normalization. The horizontal axis represents keyword ranking, and the vertical axis represents keywords frequency. Solid red line indicates the distribution of published according to the Zipf's Law. The scatter blue indicates the publication on subject matter. **(B)** Logarithm curve of keywords frequency distribution in the field of tumor vascular normalization. The horizontal axis represents the logarithm of keywords ranking, the vertical axis represents the logarithm of keywords frequency. The dotted red line indicates the distribution of published according to the Zipf's Law. The scatter blue indicates the publication on subject matter. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

frequencies in the field of tumor vascular normalization; the overall curve shows a decreasing trend, with frequency decreasing as the rank order increases. We found that the scatter plot best fit the power function $y = 78.33x^{-0.581}$, which conformed to Zipf's word frequency distribution trends. In addition, Fig. 9B shows the logarithm curve of keyword frequency distribution, and the scattered line can be approximated by the linear relationship $R^2 = 0.9747$. Therefore, the frequency pattern of keywords in the field of tumor vascular normalization was essentially consistent with Zipf's Law.

Notably, keywords encompass the major themes and topics of a publication. Therefore, we constructed a keywords network map using VOSviewer; Fig. 10A demonstrates that the keywords were grouped into five clusters (red, green, blue, yellow, and purple). Specifically, Cluster 1 (red) consisted of 13 items, including vascular normalization, immunotherapy, hypoxia, cancer, and tumor angiogenesis. Cluster 2 (green) included 12 items, such as angiogenesis, bevacizumab, VEGF, tumor vascular normalization, and biomarkers. Cluster 3 (blue) consisted of 11 items, including tumor microenvironment, chemotherapy, drug delivery, extracellular matrix, and nanoparticles. Cluster 4 (yellow) contained 7 items, including angiogenesis inhibitors, combination therapy, and tumor vessel normalization. Cluster 5 (purple) consisted of 4 items, such as cancer therapy and nanomedicine, among others.

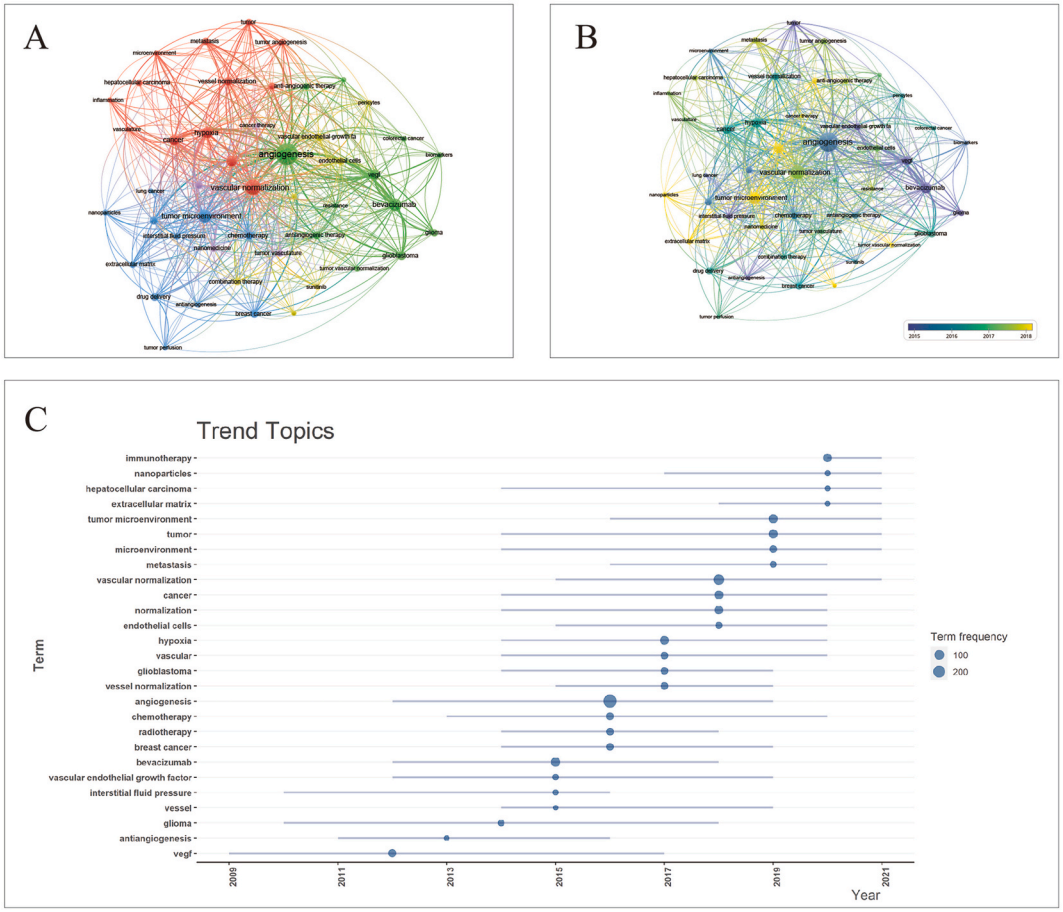

Fig. 10. **(A)** The network visualization map of keywords was produced by using a VOSviewer. **(B)** The overlay visualization map of keywords was produced by using a VOSviewer. The nodes marked blue or purple color represent the relatively earlier keywords, while yellow color represented the recent keywords. **(C)** Trend topics in the field of vascular normalization in cancer was generated by using a R-bibliometrix. The X-axis represents the year, while the Y is the cumulate occurrences of the keywords. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 10B displays the overlay visualization map of author's keywords, with blue representing the early-stage keywords and orange the more recent ones. Notably, "bevacizumab," "VEGF," "anti-angiogenesis," and "interstitial fluid pressure" were the main keywords used early on, whereas "immunotherapy," "tumor microenvironment," and "nanoparticles" emerged as hot topics recently. Additionally, the analysis of trend topic can help portray the inception and integration of trends rooted in the previous flow [35]. According to the occurrence frequency of keywords, we constructed the trend topic map using R-Bibliometrix software (the minimum word frequency = 10, words per year = 4, Fig. 10C). This findings indicated that "immunotherapy" emerged in 2020, and "nanoparticles" emerged in 2017 in the field of tumor vascular normalization. "Immunotherapy," "nanoparticles," and "extracellular matrix" had the highest frequency in 2020, whereas "tumor microenvironment" had the highest frequency in 2019.

Table 7
The top 10 key research powers with the most publication on vascular normalization in cancer.

Rank	Countries/regions	Institutions	Authors	Journals
1	Usa	Massachusetts general hospital	Jain RK	Cancer Rresearch
2	China	Harvard university	Duda DG	Clinical Cancer Research
3	Germany	Harvard medical school	Sylianopoulos T	Plos One
4	Japan	Catholic University of Louvain	Carmeliet P	Cancers
5	Italy	Sun Yat-Sen University	Fukumura D	Frontiers in Oncology
6	England	University of Oxford	Munn LL	Scientific Reports
7	France	University of Cyprus	Batcheloe TT	Journal of Controlled Release
8	Canada	University of Texas MD Anderson Cancer Center	Martin JD	Pnas
9	Belgium	Sichuan University	Huang YH	Oncotarget
10	Netherlands	Fudan University	Ganss R	British Journal of Cancer

4. Discussion

4.1. General information

As the world of information explodes, it is increasingly difficult to stay up to date with all the latest findings in a field of interest. To synthesize the global study on the function of vascular normalization in cancer research, we employed a bibliometric analysis using publications between 2003 and 2022, thereby providing a novel and comprehensive summary of the knowledge base, research trends, and emerging topics in specific study areas. A total of 1602 articles from 583 journals and 80,252 co-cited references were included in the analysis after excluding studies that did not meet the screening criteria. The top 10 key research powers with the most publications on vascular normalization in cancer are summarized in Table 7.

Academic publications are a key indicator of a field's developing trends [36]. Overall, between January 1, 2003, and October 29, 2022, publications related to vascular normalization in cancer gradually increased. A notable increase in publications in this field occurred from 2000 to 2016, with slight fluctuations yearly. This is attributed to significant scientific advances in the field throughout this period; specifically, RK Jain introduced the groundbreaking theory on vascular normalization, which has shown promising therapeutic outcomes in patients with clinical tumors. Subsequently, this theory attracted significant interest, which led to refinement in our understanding of normalized vascular structure and function. In addition, several anti-angiogenic agents have been approved by the US FDA for the treatment of cancer patients. Interestingly, although the number of publications declined slightly in 2017, 2018 saw a resurgence, possibly owing to data implying coordinated regulation with concomitant immune checkpoint blockade (ICB) and anti-angiogenesis, suggesting potential synergistic treatment strategies. However, the number of publications fell below Price's curve in the last three years, which may be due to the COVID-19 pandemic, among other reasons.

In terms of international involvement, approximately 62 countries/regions and 1916 institutions have published on vascular normalization in cancer. The cumulative sum of publications. citations and the H-index, serve as pivotal metrics indicative of the national research level and scholarly influence. As shown in Table 1 and Fig. 3, the leading 10 contributors on tumor vascular normalization include two North American (the USA and Canada), two Asian (China and Japan), and several European countries (Germany, Italy, England, France, Belgium, and the Netherlands). USA exhibited the highest H-index and quantity of publications and citations within this domain because of its robust biomedical foundation, extensive financial backing, and substantial availability of investigators and institutions.

Among the leading 10 institutions, four were from the USA, and Harvard University and Massachusetts General Hospital ranked highest in terms of citations. These findings highlight the significant contributions of the USA, Massachusetts General Hospital, and Harvard University, establishing them as leaders in the field of vascular normalization in cancer. In addition, China demonstrated notable and rapid growth, surpassing the USA in terms of publication volume since 2017. This surge may be attributed to growing healthcare demands, increased government support, and advancements in biological treatment. Furthermore, USA has fostered extensive international collaborations, particularly with China (Fig. 3). However, the cooperation between other countries, especially developing countries, is currently limited. Developing countries should encourage active participation in research, strengthen international collaborations, and disseminate high-quality academic articles for the advancement of relevant disciplines. Overall, almost all of the top 10 countries/regions and top 10 institutions are located in North America, Europe and Asia, and except for China, all are developed countries. There is a discernible correlation exists between academic productivity and economic strength, suggesting that developed nations and prestigious institutions possess a substantial advantage and exert considerable influence within the research landscape.

Lotka's Law evaluates the productivity and disciplinary attention of individual investigators. Based on Lotka's Law, RK Jain was the most productive contributor, with 75 publications, and has played a vital role in promoting tumor vascular normalization research. Notably, six of the top 10 most prolific authors were affiliated with Harvard Medical School and Massachusetts General Hospital. Interestingly, the proportion of authors that published only one article on tumor vascular normalization was 81.8%, which was higher than the predicted 60%. The results of this study indicate widespread attention has been paid to the field of vascular normalization in cancer, although the number of prolific authors was still limited, with a certain degree of independence among researchers. In terms of co-cited authors, the top 10 individuals with $\geq$30 co-citations have significantly impacted the field of vascular normalization in cancer. RK Jain held the highest rank with 2356 co-citations, followed by P Carmeliet and J Folkman. RK Jain is widely recognized for his influential contributions in introducing the concept of "vascular normalization", emphasizing the appropriate dosage of anti-angiogenic treatment. P Carmeliet has contributed to the understanding of VEGF's role in tumor angiogenesis, with implications for cancer treatment that target anti-angiogenic pathways. Initially, Folkman identified angiogenesis as one of the key procedure that promote cancer progression and metastasis. The groundbreaking discovery led to the proposal of anti-angiogenesis as a novel therapeutic approach for cancer treatment, facilitating the development of anti-angiogenic drugs for clinical use.

Examining journal publication rates and their co-citations can provide valuable insights to assist with the selection of appropriate journals for manuscript submission [37,38]. According to Bradford's Law, 27 nuclear source journals were categorized into zone 1, having published one third of the extracted articles in the field of tumor vascular normalization (Fig. 6A–Table 5). Among the top 10 journals, *Cancer Research*, *Clinical Cancer Research*, and *PLoS One* emerged as the three most productive journals in the domain (Table 4). Thus, these journals are recommended for the submission of new articles. Our findings revealed that the *Journal of Cancer Research* and *Journal of Clinical Cancer Research* have been publishing articles on vascular normalization since 2003 (Fig. 6B); we also observed a notable surge in the annual publication count for the journal *Cancers* beginning in 2018. Fig. 6C shows that *Cancer Research* emerged as the journal with the highest frequency of co-citations, followed by *PNAS*, *Nature*, *Cancer Cell*, and *Clinical Cancer Research*. These results show the positive influence that these journals have over other journals in this specific field. As a result, papers published

in these journals are more likely to be noticed, cited, and have a significant influence on the future research landscape, and prioritizing the examination of these papers is imperative to remain updated on the latest advancements. Lastly, in current journal publications, "genetics" and "molecular biology" were frequently cited in the context of "medicine," "medical," and "clinical," indicating a prevailing emphasis on clinical research.

4.2. Knowledge base

An article's significance in a particular field increases proportionally to its number of citations. Hence, citing the most influential publications can serve as a metric of knowledge within the specific field. Based on Table 6, the most cited articles included seven reviews and three basic research studies. In terms of publication timelines, three articles (two basic research studies and one review) were published between 2000 and 2005 (early stage), four were reviews published between 2011 and 2014 (middle stage), and three (two reviews and one basic research study) were published between 2017 and 2023 (recent stage).

The three papers authored by RK Jain during the early stage primarily addressed elucidating the concept and mechanism of tumor vascular normalization, as well as strategies for achieving vascular normalization. These articles are particularly noteworthy for their crucial role in advancing the field and have significantly contributed to the clinical application of VEGF receptor 2 pathway inhibition. Of these papers, the one titled "Normalization of tumor vasculature: an emerging concept in anti-angiogenic therapy" was the most frequently cited and primarily focused on reviewing emerging evidence supporting the temporarily restoration of the abnormal tumor vasculature by the administration of anti-angiogenic agents. It placed particular emphasis on VEGF signaling in achieving this normalization [11]. The second and third most co-cited papers, "Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases" and "Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors," respectively, clarified the mechanisms involved in inducing tumor vascular normalization through VEGFR2 pathway inhibition. Specifically, the former paper demonstrated increased pericyte coverage in brain tumor vessels resulting from VEGFR2 blockade using DC101, a monoclonal antibody. This increase was achieved through upregulation of angiopoietin 1 and degradation of the pathologically thickened basement membrane via matrix metalloproteinase activation. These effects created an optimal period for radiation therapy. The latter paper determined that DC101-mediated VEGF signaling pathway inhibition decreased interstitial fluid pressure, resulted in a hydrostatic pressure gradient across the vascular wall, and ultimately allowed therapeutic agents to penetrate deeper into tumors tissues [34,39]. These studies provided a solid foundation for the theory of tumor vascular normalization.

During the middle stage, four comprehensive reviews authored by RK Jain provided a thorough elucidation of the pathophysiological intricacies of tumor angiogenesis, encompassing its molecular underpinnings, functional repercussions, limitations, and potential clinical applications of tumor vascular normalization. The papers titled "Normalization of the vasculature for treatment of cancer and other diseases" and "Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases," published in 2011, offered a comprehensive overview of these topics [14,40]. In 2013, the article titled "Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers" introduced potential biomarkers for anti-VEGF resistance, including circulating soluble VEGF receptor 1 and the chemokine stromal cell-derived factor-1 alpha. Elevated pre-treatment levels of these biomarkers predict reduced effectiveness of bevacizumab in combination with chemoradiotherapy in various cancer types, including rectal carcinoma, glioblastoma, triple-negative breast cancer, hepatocellular carcinoma, and metastatic colorectal carcinoma [41]. In 2014, the article titled "Anti-angiogenesis strategies revisited: from starving tumors to alleviating hypoxia" emphasized the significance of mitigating hypoxia via the administration of anti-angiogenic agents to enhance the efficacy of tumor treatment. Additionally, the article explored alternative approaches to impede tumor angiogenesis, such as targeting endothelial cell metabolism and oncogenic pathways [42]. These reviews further elaborated on the strategies and related mechanisms of inducing tumor vascular normalization and increased the potential of its clinical application.

Considering the adverse effects associated with anti-VEGF therapy, such as an increased risk of both venous thrombosis and tumor metastasis, the 2017 publication by B Larrivée titled "Tumor angiogenesis and vascular normalization: alternative therapeutic targets" presented alternative therapeutic targets for achieving tumor vascular normalization, including angiopoietin signaling, platelet-derived growth factor-B, bone morphogenetic protein signaling, vascular endothelial-cadherin, and hypoxia-inducible factor 1alpha [9]. The 2018 *Nature* publication titled "Mutual regulation of tumor vessel normalization and immunostimulatory reprogramming" emphasized the significant impact of Th1 cells in facilitating vascular normalization. Th1 cells were found to alter the cytokine milieu, which subsequently influenced pericyte recruitment and promoted vascular normalization [43]. Consequently, the process of vascular normalization led to the recruitment of tumor-infiltrating lymphocytes, thereby altering the immune landscape in a mutually regulatory feedback loop. Additionally, the paper speculated that Th1 cells could serve as a marker for assessing the efficacies of ICB and anti-angiogenic therapies. The 2018 paper titled "Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges" by RK Jain primarily elucidated the functions of VEGF and angiopoietin 2 on fostering immune evasion and progression within tumors. Additionally, the study delved into the potential of blood vessels normalization to transition the immunosuppressive tumor microenvironment into an immunostimulatory milieu [44]. At this stage, the field of tumor vascular normalization is relatively mature, some alternative therapeutic targets have been discovered, and the potential for concomitance with immunotherapy has been explored.

Collectively, these top 10 extensively referenced sources offer a comprehensive survey of tumor vascular normalization, encompassing various underlying mechanisms, evaluating the potential advantages and constraints of clinical implementation, and contemplating future scientific and therapeutic advancements.

Despite the conclusion of the majority of the observed citation bursts, a few persist, with a predominant focus on the integration of anti-angiogenesis and immunotherapy, particularly ICB via programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1)". This observation suggests sustained progress in recent years, as depicted in Fig. 8C.

4.3. Research hotspots and frontiers

Within bibliometrics, the analysis of co-cited references and author keyword co-occurrences offer valuable perspectives on the main research trends and areas of focus, essential for a thorough understanding of the field's evolution.

A field's major themes and emerging patterns can be effectively highlighted by high frequency keywords. Five clusters were enriched after the keyword co-occurrence analysis Fig. 10A), which were named according to the Synthetic Knowledge Synthesis method [45]. Cluster 1 (red) depicted the correlation between immunotherapy and tumor vascular normalization. This cluster contained the keywords vascular normalization, immunotherapy, hypoxia, cancer, tumor angiogenesis, anti-angiogenesis, and hepatocellular carcinoma, among others. Immunotherapy has emerged as a highly hopeful strategy to prevent cancer progression [46,47], and the intricate interplay between angiogenesis and immunotherapy displays a complex relationship. An anti-angiogenic agent are capable of stimulating the immune system, thereby reducing the immunosuppressive milieu, while conversely, immunotherapy exert inhibitory effects on angiogenesis. In a preclinical investigation utilizing a murine cancer model, the combined inhibition of VEGFA and angiopoietin 2 with the bispecific antibody A2 V was found to significantly augment the therapeutic outcomes of antitumor intervention. Specifically, the administration of A2 V facilitated the perivascular accumulation of T cells, leading to normalized blood vessels, activated tumor-infiltrating $CD8^+$ T cells, and increased antigen presentation. Furthermore, A2 V in combination with anti-PD-1/PD-L1 antibodies has exhibited potential anti-tumor effects, including the prolongation of anti-angiogenesis [48]. In addition, blood vessel normalization can be achieved by cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and PD-1 ICB in various models of transplanted tumors due to increased accumulation of Th1 $CD4^+$ cells and antitumor activity. Recently, blockade of the CD93 pathway was shown to normalize tumor vascular to facilitate immunotherapy. Furthermore, anti-CTLA-4 treatment promoted the accumulating eosinophils resulting in the normalization of breast tumor blood vessels [49]. These results demonstrate the positive and influential role of immunotherapy on tumor vascular normalization. Therefore, researchers or clinicians should consider the combination of both approaches to enhance the anti-tumor effect, when anti-tumor angiogenesis or immunotherapy drugs alone demonstrate limited efficacy or encounter drug resistance.

Cluster 2 (green) was associated with bevacizumab and its anti-cancer effects, encompassing keywords such as angiogenesis, bevacizumab, VEGF, anti-angiogenic therapy, tumor vascular normalization, and glioma. VEGF is a key factor in cancer angiogenesis, and bevacizumab, a VEGF inhibitor, is commonly used to promote tumor vascular normalization. Lower doses of bevacizumab used have the ability to temporarily normalize cancer blood vessels, decrease blood vessel density, and enhance perfusion, establishing a therapeutic window for improved drug delivery [40]. Compared with atezolizumab (a PD-L1 inhibitor) alone, combination therapy with bevacizumab increased progression-free survival (PFS) of patients suffer from Hepatocellular carcinoma [50]. An atezolizumab and bevacizumab trial involving metastatic renal cell carcinoma showed similar results [51], demonstrating the key role of bevacizumab on tumor vascular normalization.

Cluster 3 (blue) concerned the topic of tumor microenvironment, included the keywords tumor microenvironment, tumor perfusion, extracellular matrix, drug delivery, nanoparticles, and chemotherapy, among others. This aligns with the mounting body of evidence establishing the tumor microenvironment as a intricate milieu that might play a contributory role in cancer growth, angiogenesis, and metastasis [52]. The tumor microenvironment is typically characterized by hypoxia and acidic pH levels, these conditions are associated with aberrant vascular structure. Hypoxia triggers an overexpression of proangiogenic factors, particularly VEGF [53–55], and the dysregulation of pro- and anti-angiogenic factors fosters the abnormal development of tumor blood vessels. Moreover, the acidic nature of the tumor microenvironment has been found to promote immunosuppression. For example, acidic pH levels inhibited $CD8^+$ T cell differentiation and function by interferon-gamma (IFN-γ) inactivation and suppression of tumor necrosis factor alpha (TNF-α), resulting in a state of anergy in those cells [56–58]. Additionally, acidic pH levels activated and transformed tumor-associated macrophages (TAMs) into pro-tumor M2 cells [59]. However, hypoxia and acidic microenvironment can be directly mitigated by normalizing the tumor vascular system, which can promote the transformation of TAMs into anti-tumor M1 type and facilitate $CD4^+$ and $CD8^+$ T cells infiltration [60]. Interestingly, scholar T Nomura has described an immunotherapy strategy utilizing dendritic cells (DCs) in a mouse with B16/BL6 melanoma model; in this model, lung metastasis was effectively suppressed by prophylactic vaccination with DCs that were pulsed with lysates of tumor endothelial cells isolated from metastatic lung cancers [61]. These studies show that the tumor microenvironment is a focal point on tumor vascular normalization. Thus, in animal models or cell culture studies, the addition of specific immune cells, like DCs, $CD8^+$ T cells, eosinophils, along with cytokines like TNF-γ and TNF-α, could be regarded as a promising approach for stimulating tumor vascular normalization.

Cluster 4 (yellow) summarized the use of anti-angiogenic combination therapies to facilitate tumor vascular normalization. The cluster included the keywords angiogenesis inhibitors, combination therapy, tumor vessel normalization, and endothelial cells, among others. At present, several therapeutic agents have been shown to induce tumor vascular normalization, including bevacizumab, small-molecular multikinase inhibitors, and PD-1 inhibitors. In combination, these drugs have a synergistic effect on vascular normalization. For instance, the combination of anlotinib and PD-1 checkpoint inhibitors helped to prolong the duration of vascular normalization, eventually inducing neuroblastoma regression [62]. The combination of astragali polysaccharide and curcumin induced vascular normalization, thereby leading to the inhibition of hepatocellular carcinoma progression [63]. Consequently, a growing quantity of clinical trials investigating the effectiveness of combination therapies have been conducted in recent years. Compared with the control group, patients receiving atezolizumab and bevacizumab-based chemotherapy exhibited significantly improved both overall survival

and PFS in a phase 3 clinical trial designed IMpower150 (NCT02366143) [64]. Similarly, a phase 3 trial (NCT02684006) provided evidence supporting the enhanced therapeutic efficacy of avelumab plus axitinib in patients suffer from RCC, demonstrating significant improvements in median PFS and objective response rates compared with sunitinib treatment [65]. Thus, the future research emphasis on tumor vascular normalization is no longer confined to inhibiting tumor angiogenesis alone. To enhance treatment efficacy, further exploration of combination therapies is recommended, particularly those involving immunotherapies such as immune checkpoint inhibitors.

Cluster 5 (purple) represented the role of nanomedicine in tumor vascular normalization. This cluster contained the keywords cancer therapy, nanomedicine, normalization, and tumor vasculature. Abnormal vascular system in the tumor contributes to the formation of the malignant tumor milieu, providing a foundation for tumor cell growth and metastasis. Tumor vascular normalization corrects this abnormal state, which may recover the normal tumor blood vessels function, enhance perfusion and oxygen index, improve the delivery and effectiveness of drugs. Nanomedicines, as perfect vehicles with flexible and modifiable biomaterials, can more easily restore cancer vessels, perform combined delivery, and modify the tumor immunosuppressive environment. One such example features nitric oxide (NO), which can regulate angiogenesis and maintains vascular normalization; low-dose NanoNO, a nanoscale carrier, has been shown to normalize cancer vascular through delivering NO and shifting the immunosuppressive tumor microenvironment into an immunostimulatory one [66]. Similarly, gold nanoparticles were shown to deliver recombinant human endostatin to normalize tumor vasculature and improve cancer therapy [67]. Therefore, nanoparticle therapy is a promising addition to current vascular-targeting strategies. Moreover, the combination therapy strategies, based on nanotechnology, involve co-delivering various vascular-normalizing drugs (cluster 4) to maximize the "starve tumor" effect and combining them with immunotherapeutic drugs in a single nanoplatform. This approach has the capability to increase the anti-tumor impact and offer an option for preclinical targeted cancer therapy. Currently, numerous nanomedicines aimed at normalizing tumor blood vessels have been extensively investigated in preclinical studies. However, the clinical use is still limited, primarily due to the shortage of specific molecules that target cancer blood vessels, making it difficult for them to achieve full targeting of tumor blood vessels [68].

Notably, Fig. 10B demonstrates that these identified research topics, including "immunotherapy," "tumor microenvironment," and "nanoparticles," emerged as research focal topics in recent years. Furthermore, the trend topic analysis showed that the term of "nanoparticles" emerged in 2017, and "immunotherapy" in 2020 on tumor vascular normalization research. "Immunotherapy," "nanoparticles," "extracellular matrix" had the highest frequency of use in 2020, whereas "tumor microenvironment" peaked in 2019. These results indicate that investigators increasingly focused on these keywords in 2019 and 2020. These findings align with the results obtained from VOSviewer.

Furthermore, the evolution of literature clusters over time (Fig. 8B) revealed that initial study primarily concentrated on the pathological attributes of vascular normalization, including "interstitial fluid pressure," "tumor hypoxia," "acidosis," and "capillary remodeling," whereas current research hotspots have shifted to "immunotherapy," "metabolism," "angiogenesis," and "mechano-medicine." Thus, earlier studies primarily focused on elucidating the underlying characteristics of tumor vascular normalization, and significant advancements have been achieved in this field. Currently, abnormal blood vessels have been identified as playing a key role in inducing hypoxia and acidosis within the tumor microenvironment. Under these adverse environmental conditions, tumor cells and stromal cells may modify their metabolism to satisfy the increased energy requirements and drive accelerated tumor growth, thereby antagonizing the blood vessels normalization effect induced by anti-angiogenic agents. However, recent advances have confirmed that the metabolism of tumor endothelial cells can be reprogrammed. Targeting endothelial metabolic pathways, such as those involving phosphoglycerate dehydrogenase or through blocking the glycolytic activator pfkfb3, can induce tumor vascular normalization [69–71]. These findings indicate that targeting endothelial metabolic pathways is a frontier area in the field of tumor vascular normalization. Although basic research and clinical diagnosis and treatment of tumors have focused on unveiling their complex biological features, the exploration of their physical properties has been relatively limited. However, tumor growth causes notable physical changes in tumors and surrounding tissues, highlighting the increasing importance of studying the physical characteristics of tumors. Falling under the topic of mechanomedicine, the extracellular matrix drives the generation of solid pressure, resulting in increased tumor hardness and structural changes, which in turn promotes tumor development [72]. Recent advances have confirmed that mechanical stress plays a key role in tumor growth and angiogenesis, it can also mediate resistance to anti-angiogenic therapy [72–74]. This provides a new strategy for inducing tumor vascular normalization. Therefore, the concept of "mechanomedicine" can be considered a new paradigm in the knowledge field of tumor vascular normalization, which will undoubtedly offer an invaluable option for clinical cancer treatment in the future.

With the continuous technological advancement of anti-angiogenic therapy, research on the application of tumor blood vessels normalization has also significantly advanced. However, many urgent concerns remain to be solved, some of which are as follows. 1) High-dose and long-duration anti-angiogenic treatment or concomitance with immunotherapeutic drugs cannot completely extend the vascular normalization window. Thus, there is a crucial necessity to refine the dosage, duration, and order of agent usage. 2) Given the inherent heterogeneity of tumors, the responses of individual patients to different anti-angiogenic inhibitors can vary significantly. Hence, identifying and validating reliable and highly sensitive biomarkers is crucial. These biomarkers can play a pivotal role in guiding clinical treatment strategies and ensure their effectiveness. 3) Specific target molecules for tumor blood vessels must be identified to enhance drug delivery efficiency in nanomedicine and achieve complete targeting of the tumor vasculature. 4) Although various technologies and strategies have been devised to verify the effectiveness of anti-angiogenic therapy, and identify the optimal time frame for tumor vascular normalization, a consensus remains elusive. Further clinical trials and comprehensive data are required to confirm validity of these techniques. In addition, new technologies, such as liquid biopsy or imaging technologies, require further exploration to guide precision therapy. 5) The mechanisms of drug resistance and the side effects need to be addressed. 6) The multiscale mechanical characteristics of tumors also need to be explored. These challenges highlight the urgent need for

multidisciplinary collaborations to overcome technical and application barriers. Through addressing these challenges, the realm of tumor vascular normalization can unleash its complete potential to transform the landscape of cancer therapy.

Currently, vascular normalization is increasingly being recognized as an adjunctive treatment approach for cancer and other vascular disorders. A recent bibliometric study showed that most publications on VEGF therapy are in the field of ophthalmology, followed by oncology and other diseases [75]. Another bibliometric study identified endovascular therapy as a prominent area of focus in research on vascular calcification [76]. In addition, a recent study proposal suggests that vascular normalization could potentially improve the vascular system of patients with COVID-19 [77]. Although many articles and reviews have been published on the topic of tumor vascular normalization, most publications have focused on the mechanisms and application of vascular normalization in cancer, and the efficacy of anti-angiogenic drugs in combination with other drugs. Thus, we aimed to clarify and synthesize the research pertaining to tumor vascular normalization, covering trends in publication, key research powers, and focal investigative points. These discoveries enable the researchers to identify new concepts and directions that will propel future research on tumor vascular normalization.

5. Limitations

This study represents the first bibliometric attempt to provide a comprehensive overview of the current state and progress on tumor vascular normalization. The findings of this study could be a valuable source for healthcare professionals and researchers engaged in this particular field. Furthermore, we employed bibliometric tools to comprehensively assess the existing literature from various perspectives. Nevertheless, we acknowledge that there are multiple limitations. First, this study restricted the inclusion criteria to articles published between 2003 and 2022; furthermore, the literature extracted for 2022 was incomplete, potentially resulting in the exclusion of key publications or unpublished areas of interest. Consequently, conducting subsequent analyses with broader inclusion criteria is imperative to ensure a more objective evaluation of the findings. Second, our literature search exclusively relied on English language sources, potentially inadvertently omitting articles published in other languages. Additionally, exclusively utilizing the WoSCC database may have excluded relevant studies available in other databases, resulting in a selection bias. Third, the search bias produced by several Boolean operators “OR” may lead to the omission of few certain scholarly publications within this field. Fourth, despite utilizing multiple software tools to analyze various content, the analysis fell short of offering a complete portrayal of the articles pertaining to vascular normalization in cancer. Nevertheless, we maintain that this literature-based bibliometric study can, to a considerable extent, enable scholars to grasp the research focal points and evolutionary patterns concerning vascular normalization in the context of cancer.

6. Conclusions

The present study employed bibliometric approaches to systematically collect and analyze worldwide publications in the field of tumor vascular normalization from the past two decades, encompassing international collaborations, distribution of academic output, focal areas of research, and emerging trends. These results are vital to aid in accurately identifying areas of inquiry to make relevant advancements in the field. According to this report, the global distribution of scientific output is currently uneven, with developed countries/regions dominating the field, and USA is prominent with their superior academic impact. Furthermore, our study identified present research hotspots, including immunotherapy, tumor microenvironment, and nanomedicine, as well as emerging hotspots, including metabolism and mechanomedicine. With continued scientific, medical, technological, and societal progress, the field of tumor vascular normalization is expected to make significant advances, thereby greatly facilitating research discoveries and translation of tangible clinical applications.

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Data availability statement

Data included in this study has been sourced and obtained from the publicly accessible database. The data referenced within the article can be accessed through the corresponding author upon request if needed.

Ethics approval and consent to participate

Ethical approval was deemed needless for this study as the bibliometric analysis was conducted using data extracted directly from databases, without any involvement of human or animal subjects.

CRediT authorship contribution statement

Hanghang Xie: Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Data curation, Conceptualization. **Shan Wang:** Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology, Data curation. **Dongling Niu:** Writing – review & editing, Writing – original draft, Visualization, Software, Resources,

Methodology, Investigation, Data curation. **Chao Yang:** Visualization, Software, Methodology, Investigation, Data curation. **Hongmei Bai:** Visualization, Software, Methodology, Investigation, Data curation. **Ting Lei:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Data curation. **Hongli Liu:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

VEGF	Vascular Endothelial Growth Factor
FDA	Food and Drug Administration
WoSCC	Web of Science Core Collection
SCIE	Science Citation Index Expanded
TLS	Total Link Strength
USA	United States of America
PD-1	Programmed cell Death protein 1
PD-L1	Programmed Death Ligand 1
PFS	Progression-Free Survival
DCs	Dendritic Cells
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
NO	Nitric Oxide

References

[1] J. Folkman, E. Merler, C. Abernathy, G. Williams, Isolation of a tumor factor responsible for angiogenesis, J. Exp. Med. 133 (2) (1971) 275–288. http://doi:10.1084/jem.133.2.275.
[2] N. Ferrara, R.S. Kerbel, Angiogenesis as a therapeutic target, Nature 438 (7070) (2005) 967–974. http://doi:10.1038/nature04483.
[3] R.S. Kerbel, Tumor angiogenesis, N. Engl. J. Med. 358 (19) (2008) 2039–2049. http://doi:10.1056/NEJMra0706596.
[4] M. Potente, H. Gerhardt, P. Carmeliet, Basic and therapeutic aspects of angiogenesis, Cell 146 (6) (2011) 873–887. http://doi:10.1016/j.cell.2011.08.039.
[5] C. Verdelli, V. Vaira, S. Corbetta, Parathyroid tumor microenvironment, Adv. Exp. Med. Biol. 1226 (2020) 37–50. http://doi:10.1007/978-3-030-36214-0_3.
[6] P.C. Maisonpierre, C. Suri, P.F. Jones, S. Bartunkova, S.J. Wiegand, C. Radziejewski, et al., Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis, Science 277 (5322) (1997) 55–60. http://doi:10.1126/science.277.5322.55.
[7] A.P. Laddha, Y.A. Kulkarni, VEGF and FGF-2: promising targets for the treatment of respiratory disorders, Respir. Med. 156 (2019) 33–46. http://doi:10.1016/j.rmed.2019.08.003.
[8] J. Tao, G. Yang, W. Zhou, J. Qiu, G. Chen, W. Luo, et al., Targeting hypoxic tumor microenvironment in pancreatic cancer, J. Hematol. Oncol. 14 (1) (2021) 14. http://doi:10.1186/s13045-020-01030-w.
[9] C. Viallard, B. Larrivee, Tumor angiogenesis and vascular normalization: alternative therapeutic targets, Angiogenesis 20 (4) (2017) 409–426. http://doi:10.1007/s10456-017-9562-9.
[10] S.A. Patel, M.B. Nilsson, X. Le, T. Cascone, R.K. Jain, J.V. Heymach, Molecular mechanisms and future implications of VEGF/VEGFR in cancer therapy, Clin. Cancer Res. 29 (1) (2023) 30–39. http://doi:10.1158/1078-0432.CCR-22-1366.
[11] R.K. Jain, Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy, Science 307 (5706) (2005) 58–62. http://doi:10.1126/science.1104819.
[12] R.K. Jain, Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy, Nat. Med. 7 (9) (2001) 987–989. http://doi:10.1038/nm0901-987.
[13] S.S. Chae, W.S. Kamoun, C.T. Farrar, et al., Angiopoietin-2 interferes with anti-VEGFR2-induced vessel normalization and survival benefit in mice bearing gliomas, Clin. Cancer Res. 16 (14) (2010) 3618–3627, https://doi.org/10.1158/1078-0432.CCR-09-3073.
[14] S. Goel, D.G. Duda, L. Xu, L.L. Munn, Y. Boucher, D. Fukumura, et al., Normalization of the vasculature for treatment of cancer and other diseases, Physiol. Rev. 91 (3) (2011) 1071–1121. http://doi:10.1152/physrev.00038.2010.
[15] K. Wang, Q. Chen, N. Liu, J. Zhang, X. Pan, Recent advances in, and challenges of, anti-angiogenesis agents for tumor chemotherapy based on vascular normalization, Drug Discov. Today 26 (11) (2021) 2743–2753. http://doi:10.1016/j.drudis.2021.07.024.
[16] Z. Pei, S. Chen, L. Ding, J. Liu, X. Cui, F. Li, et al., Current perspectives and trend of nanomedicine in cancer: a review and bibliometric analysis, J. Contr. Release 352 (2022) 211–241. http://doi:10.1016/j.jconrel.2022.10.023.
[17] Y. Su, Z. Ruan, R. Wang, S. Hao, Y. Tang, X. Huang, et al., Knowledge mapping of targeted immunotherapy for myasthenia gravis from 1998 to 2022: a bibliometric analysis, Front. Immunol. 13 (2022) 998217. http://doi:10.3389/fimmu.2022.998217.
[18] P. Kokol, H. Blazun Vosner, J. Zavrsnik, Application of bibliometrics in medicine: a historical bibliometrics analysis, Health Inf. Libr. J. 38 (2) (2021) 125–138, https://doi.org/10.1111/hir.12295.
[19] N.J. van Eck, L. Waltman, Software survey: VOSviewer, a computer program for bibliometric mapping, Scientometrics 84 (2) (2010) 523–538. http://doi:10.1007/s11192-009-0146-3.
[20] Y. Yu, Y. Li, Z. Zhang, Z. Gu, H. Zhong, Q. Zha, et al., A bibliometric analysis using VOSviewer of publications on COVID-19, Ann. Transl. Med. 8 (13) (2020) 816. http://doi:10.21037/atm-20-4235.

[21] C. Chen, R. Dubin, M.C. Kim, Emerging trends and new developments in regenerative medicine: a scientometric update (2000 - 2014), Expet Opin. Biol. Ther. 14 (9) (2014) 1295–1317. http://doi:10.1517/14712598.2014.920813.

[22] M.B. Synnestvedt, C. Chen, J.H. Holmes, CiteSpace II: visualization and knowledge discovery in bibliographic databases, AMIA Annu Symp Proc 2005 (2005) 724–728.

[23] Ebrahim S. Ale, A. Ashtari, M. Zamani Pedram, N. Ale Ebrahim, A. Sanati-Nezhad, Publication trends in exosomes nanoparticles for cancer detection, Int. J. Nanomed. 15 (2020) 4453–4470. http://doi:10.2147/IJN.S247210.

[24] M.E. Falagas, E.I. Pitsouni, G.A. Malietzis, G. Pappas, Comparison of PubMed, scopus, web of science, and google scholar: strengths and weaknesses, Faseb. J. 22 (2) (2008) 338–342. http://doi:10.1096/fj.07-9492LSF.

[25] L. Ke, C. Lu, R. Shen, T. Lu, B. Ma, Y. Hua, Knowledge mapping of drug-induced liver injury: a scientometric investigation (2010-2019), Front. Pharmacol. 11 (2020) 842. http://doi:10.3389/fphar.2020.00842.

[26] J. Zhao, G. Yu, M. Cai, X. Lei, Y. Yang, Q. Wang, et al., Bibliometric analysis of global scientific activity on umbilical cord mesenchymal stem cells: a swiftly expanding and shifting focus, Stem Cell Res. Ther. 9 (1) (2018) 32. http://doi:10.1186/s13287-018-0785-5.

[27] D.D.S. Price, A general theory of bibliometric and other cumulative advantage processes, J. Am. Soc. Inf. Sci. 27 (1976) 292–306, https://doi.org/10.1002/asi.4630270505.

[28] N. Kushairi, A. Ahmi, Flipped classroom in the second decade of the millenia: a bibliometrics analysis with Lotka's law, Educ. Inf. Technol. 26 (2021) 4401–4431, https://doi.org/10.1007/s10639-021-10457-8.

[29] C.E. Nash-Stewart, L.M. Kruesi, C.B. Del Mar, Does Bradford's law of scattering predict the size of the literature in cochrane reviews? J. Med. Libr. Assoc. JMLA. 100 (2012) 135–138, https://doi.org/10.3163/1536-5050.100.2.013.

[30] G.K. Zipf, Selected Studies of the Principle of Relative Frequency in Language, Harvard University Press, Cambridge, MA, USA, 2013.

[31] Z. Shen, H. Wu, Z. Chen, J. Hu, J. Pan, J. Kong, T. Lin, The global research of artificial intelligence on prostate cancer: a 22-year bibliometric analysis, Front. Oncol. 12 (2022) 843735, https://doi.org/10.3389/fonc.2022.843735.

[32] T. Liu, L. Yang, H. Mao, F. Ma, Y. Wang, Y. Zhan, Knowledge domain and emerging trends in podocyte injury research from 1994 to 2021: a bibliometric and visualized analysis, Front. Pharmacol. 12 (2021) 772386. http://doi:10.3389/fphar.2021.772386.

[33] K. Min, Y. Wu, S. Wang, H. Yang, H. Deng, J. Wei, et al., Developmental trends and research hotspots in bronchoscopy anesthesia: a bibliometric study, Front. Med. 9 (2022) 837389. http://doi:10.3389/fmed.2022.837389.

[34] F. Winkler, S.V. Kozin, R.T. Tong, S.S. Chae, M.F. Booth, I. Garkavtsev, et al., Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases, Cancer Cell 6 (6) (2004) 553–563. http://doi:10.1016/j.ccr.2004.10.011.

[35] Z. Dai, S. Xu, X. Wu, R. Hu, H. Li, H. He, et al., Knowledge mapping of multicriteria decision analysis in healthcare: a bibliometric analysis, Front. Public Health 10 (2022) 895552. http://doi:10.3389/fpubh.2022.895552.

[36] K. Cheng, Q. Guo, Z. Shen, W. Yang, Y. Wang, Z. Sun, et al., Bibliometric analysis of global research on cancer photodynamic therapy: focus on nano-related research, Front. Pharmacol. 13 (2022) 927219. http://doi:10.3389/fphar.2022.927219.

[37] H. Wu, Y. Li, L. Tong, Y. Wang, Z. Sun, Worldwide research tendency and hotspots on hip fracture: a 20-year bibliometric analysis, Arch. Osteoporosis 16 (1) (2021) 73. http://doi:10.1007/s11657-021-00929-2.

[38] B. Shao, Y.F. Qin, S.H. Ren, Q.F. Peng, H. Qin, Z.B. Wang, et al., Structural and temporal dynamics of mesenchymal stem cells in liver diseases from 2001 to 2021: a bibliometric analysis, Front. Immunol. 13 (2022) 859972. http://doi:10.3389/fimmu.2022.859972.

[39] R.T. Tong, Y. Boucher, S.V. Kozin, F. Winkler, D.J. Hicklin, R.K. Jain, Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors, Cancer Res. 64 (11) (2004) 3731–3736. http://doi:10.1158/0008-5472.CAN-04-0074.

[40] P. Carmeliet, R.K. Jain, Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases, Nat. Rev. Drug Discov. 10 (6) (2011) 417–427. http://doi:10.1038/nrd3455.

[41] R.K. Jain, Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers, J. Clin. Oncol. 31 (17) (2013) 2205–2218. http://doi:10.1200/JCO.2012.46.3653.

[42] R.K. Jain, Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia, Cancer Cell 26 (5) (2014) 605–622. http://doi:10.1016/j.ccell.2014.10.006.

[43] L. Tian, A. Goldstein, H. Wang, H.C. Lo, I.S. Kim, T. Welte, et al., Mutual regulation of tumour vessel normalization and immunostimulatory reprogramming, Nature 544 (7649) (2017) 250–254. http://doi:10.1038/nature21724.

[44] D. Fukumura, J. Kloepper, Z. Amoozgar, D.G. Duda, R.K. Jain, Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges, Nat. Rev. Clin. Oncol. 15 (5) (2018) 325–340. http://doi:10.1038/nrclinonc.2018.29.

[45] Peter Kokol, Synthetic knowledge Synthesis in hospital libraries, J. Hosp. Librarian. 24 (1) (2024) 10–17. http://doi:10.1080/15323269.2023.2291282.

[46] I. Mellman, G. Coukos, G. Dranoff, Cancer immunotherapy comes of age, Nature 480 (7378) (2011) 480–489. http://doi:10.1038/nature10673.

[47] M. Dougan, G. Dranoff, S.K. Dougan, Cancer immunotherapy: beyond checkpoint blockade, Annu. Rev. Cell Biol. 3 (1) (2019) 55–75. http://doi:10.1146/annurev-cancerbio-030518-055552.

[48] M. Schmittnaegel, N. Rigamonti, E. Kadioglu, C. Antonino, C.W. Rmili, A. Kiialainen, et al., Dual angiopoietin-2 and VEGFA inhibition elicits antitumor immunity that is enhanced by PD-1 checkpoint blockade, Sci. Transl. Med. 9 (385) (2017) eaak9670. http://doi:10.1126/scitranslmed.aak9670.

[49] Y. Sun, W. Chen, R.J. Torphy, S. Yao, G.F. Zhu, R.G. Lin, Blockade of the CD93 pathway normalizes tumor vasculature to facilitate drug delivery and immunotherapy, Sci. Transl. Med. 13 (2021). http://doi:10.1126/scitranslmed.abc8922.

[50] M.S. Lee, B.-Y. Ryoo, C.-H. Hsu, K. Numata, S. Stein, W. Verret, et al., Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study, Lancet Oncol. 21 (6) (2020) 808–820. http://doi:10.1016/S1470-2045(20)30156-X.

[51] T. Powles, M.B. Atkins, B. Escudier, R.J. Motzer, B.I. Rini, L. Fong, et al., Efficacy and safety of atezolizumab plus bevacizumab following disease progression on atezolizumab or sunitinib monotherapy in patients with metastatic renal cell carcinoma in IMmotion150: a randomized phase 2 clinical trial, Eur. Urol. 79 (2021) 665–673. http://doi:doi:10.1016/j.eururo.2021.01.003.

[52] J. Majidpoor, K. Mortezaee, Angiogenesis as a hallmark of solid tumors - clinical perspectives, Cell. Oncol. 44 (4) (2021) 715–737. http://doi:10.1007/s13402-021-00602-3.

[53] S. Rey, G.L. Semenza, Hypoxia-inducible factor-1-dependent mechanisms of vascularization and vascular remodelling, Cardiovasc. Res. 86 (2) (2010) 236–242. http://doi:10.1093/cvr/cvq045.

[54] L. Schito, G.L. Semenza, Hypoxia-inducible factors: master regulators of cancer progression, Trends Cancer 2 (12) (2016) 758–770. http://doi:10.1016/j.trecan.2016.10.016.

[55] T. Stylianopoulos, L.L. Munn, R.K. Jain, Reengineering the physical microenvironment of tumors to improve drug delivery and efficacy: from mathematical modeling to bench to bedside, Trends Cancer 4 (4) (2018) 292–319. http://doi:10.1016/j.trecan.2018.02.005.

[56] S. Damgaci, A. Ibrahim-Hashim, P.M. Enriquez-Navas, S. Pilon-Thomas, A. Guvenis, R.J. Gillies, Hypoxia and acidosis: immune suppressors and therapeutic targets, Immunology 154 (3) (2018) 354–362. http://doi:10.1111/imm.12917.

[57] A. Calcinotto, P. Filipazzi, M. Grioni, et al., Modulation of microenvironment acidity reverses energy in human and murine tumor-infiltrating T lymphocytes, Cancer Res. 72 (11) (2012) 2746–2756. http://doi:10.1158/0008-5472.CAN-11-1272.

[58] I. Kareva, P. Hahnfeldt, The emerging "Hallmarks" of metabolic reprogramming and immune evasion: distinct or linked? Cancer Res. 73 (9) (2013) 2737–2742. http://doi:10.1158/0008-5472.CAN-12-3696.

[59] T. Bohn, S. Rapp, N. Luther, M. Klein, T.-J. Bruehl, N. Kojima, et al., Tumor immunoevasion via acidosis-dependent induction of regulatory tumor-associated macrophages, Nat. Immunol. 19 (12) (2018) 1319–1329. http://doi:10.1038/s41590-018-0226-8.

[60] Y. Huang, J. Yuan, E. Righi, W.S. Kamoun, M. Ancukiewica, J. Nezivar, et al., Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy, Proc. Natl. Acad. Sci. U.S.A. 109 (43) (2012) 17561. http://doi:10.1073/pnas.1215397109.
[61] T. Nomura, M. Yamakawa, T. Shimaoka, T. Hirai, N. Koizumi, K. Maruyama, et al., Development of dendritic cell-based immunotherapy targeting tumor blood vessels in a mouse model of lung metastasis, Biol. Pharm. Bull. 42 (4) (2019) 645–648. http://doi:10.1248/bpb.b18-00737.
[62] Y. Su, B. Luo, Y. Lu, et al., Anlotinib induces a T cell-inflamed tumor microenvironment by facilitating vessel normalization and enhances the efficacy of PD-1 checkpoint blockade in Neuroblastoma, Clin. Cancer Res. 28 (2022) 793–809. http://doi:10.1158/1078-0432.CCR-21-2241.
[63] D. Tang, S. Zhang, X. Shi, et al., Combination of astragali polysaccharide and curcumin improves the morphological structure of tumor vessels and induces tumor vascular normalization to inhibit the growth of hepatocellular carcinoma, Integr. Cancer Ther. (2019) 18. http://doi:10.1177/1534735418824408.
[64] M.A. Socinski, R.M. Jotte, F. Cappuzzo, F. Orlandi, D. Stroyakovskiy, N. Nogami, et al., Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC, N. Engl. J. Med. 378 (24) (2018) 2288–2301. http://doi:10.1056/NEJMoa1716948.
[65] R.J. Motzer, K. Penkov, J. Haanen, B. Rini, L. Albiges, M.T. Campbell, et al., Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, N. Engl. J. Med. 380 (12) (2019) 1103–1115. http://doi:10.1056/NEJMoa1816047.
[66] Y.C. Sung, P.R. Jin, L.A. Chu, F.F. Hsu, M.R. Wang, C.C. Chang, et al., Delivery of nitric oxide with a nanocarrier promotes tumour vessel normalization and potentiates anti-cancer therapies, Nat. Nanotechnol. 14 (12) (2019) 1160. http://doi:10.1038/s41565-019-0570-3.
[67] W. Li, X. Zhao, B. Du, X. Li, S. Liu, X.-Y. Yang, et al., Gold nanoparticle–mediated targeted delivery of recombinant human endostatin norMalizes tumour vasculature and improves cancer therapy, Sci. Rep. 6 (1) (2016) 30619. http://doi:10.1038/srep30619.
[68] C.L. Wang, J.C. Xu, Y.L. Zhang, G.J. Nie, Emerging nanotechnological approaches to regulating tumor vasculature for cancer therapy, J. Contr. Release 362 (2023) 647–666. http://doi:10.1016/j.jconrel.2023.09.017.
[69] M. Garcia-Caballero, L. Sokol, A. Cuypers, P. Carmeliet, Metabolic reprogramming in tumor endothelial cells, Int. J. Mol. Sci. 23 (2022) 11052. http://doi:10.3390/ijms231911052.
[70] D. Zhang, A.M. Li, G. Hu, et al., PHGDH-mediated endothelial metabolism drives glioblastoma resistance to chimeric antigen receptor T cell immunotherapy, Cell Metabol. 35 (3) (2023) 517–534. e8. http://doi:10.1016/j.cmet.2023.01.010.
[71] A.R. Cantelmo, L.C. Conradi, A. Brajic, J. Goveia, J. Kalucka, A. Pircher, et al., Inhibition of the glycolytic activator PFKFB3 in endothelium induces tumor vessel normalization, impairs metastasis, and improves chemotherapy, Cancer Cell 30 (6) (2016) 968–985. http://doi:10.1016/j.ccell.2016.10.006.
[72] H.T. Nia, L.L. Munn, R.K. Jain, Physical traits of cancer, Science 370 (6516) (2020) eaaz0868, https://doi.org/10.1126/science.aaz0868. http://doi:10.1126/science.aaz0868.
[73] M.R. Zanotelli, C.A. Reinhart-King, Mechanical forces in tumor angiogenesis, Adv. Exp. Med. Biol. 1092 (2018) 91–112. http://doi:10.1007/978-3-319-95294-9_6.
[74] D. Sacks, B. Baxter, B.C.V. Campbell, J.S. Carpenter, C. Cognard, D. Dippel, et al., Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke, Int. J. Stroke 13 (6) (2018) 612–632, https://doi.org/10.1177/1747493018778713. http://doi:10.1177/1747493018778713.
[75] A.W.K. Yeung, M.M. Abdel-Daim, A.I. Abushouk, K. Kadonosono, A literature analysis on anti-vascular endothelial growth factor therapy (anti-VEGF) using a bibliometric approach, Naunyn-Schmiedeberg's Arch. Pharmacol. 392 (2019) 393–403. http://doi:10.1007/s00210-019-01629-y.
[76] Q. Dong, Q.C. Liang, Y. Chen, et al., Bibliometric and visual analysis of vascular calcification research, Front. Pharmacol. (2021) 12. http://doi:10.3389/fphar.2021.690392.
[77] L.L. Munn, T. Stylianopoulos, N.K. Jain, C. Corey Hardin, M.J. Khandekar, R.K. Jain, Vascular normalization to improve treatment of COVID-19: lessons from treatment of cancer, Clin. Cancer Res. 27 (10) (2021) 2706–2711. http://doi:10.1158/1078-0432.CCR-20-4750.